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# Brain

A JOURNAL OF NEUROLOGY

VOLUME 110 · PART IV · AUGUST 1987

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# CRITICAL ILLNESS POLYNEUROPATHY

## A COMPLICATION OF SEPSIS AND MULTIPLE ORGAN FAILURE

by DOUGLAS W. ZOCHODNE,<sup>1</sup> CHARLES F. BOLTON,<sup>1</sup>  
GEORGE A. WELLS,<sup>4</sup> JOSEPH J. GILBERT,<sup>1,2</sup> ANGELIKA F. HAHN,<sup>1</sup>  
JOHN D. BROWN<sup>1</sup> and WILLIAM A. SIBBALD<sup>3</sup>

(From the <sup>1</sup>Departments of Clinical Neurological Sciences, <sup>2</sup>Pathology, <sup>3</sup>Internal Medicine, and  
<sup>4</sup>Statistics and Actuarial Sciences, Victoria Hospital, University of Western Ontario, London, Ontario,  
Canada)

### SUMMARY

Nineteen patients developed polyneuropathy complicating critical illness. They had been admitted to a critical care unit following intubation for cardiac or pulmonary disease and had developed sepsis and multiple organ failure. Approximately one month following intubation, failure to wean from the ventilator and limb weakness prompted neurological referral. Examination disclosed weakness and wasting of muscles and impaired tendon reflexes in most, but not all, patients. Electrophysiological studies in 17 patients revealed attenuated compound muscle and sensory nerve action potential amplitudes and widespread denervation on needle electromyography. Autopsy in 9 patients who died of their critical illness revealed widespread primary axonal degeneration of motor and sensory fibres, with extensive denervation atrophy of limb and respiratory muscles. Survivors recovered from the polyneuropathy three to six months following discharge.

Seventeen of the patients were segregated by electrophysiological criteria into mild (8) and severe (9) polyneuropathy categories. An analysis of these two groups failed to reveal putative metabolic, drug, nutritional or toxic factors that might be responsible for the polyneuropathy. Our studies suggest that the mechanism may be a fundamental defect, still unknown, which causes dysfunction of all organ systems in this syndrome.

### INTRODUCTION

'The constitutional disturbance is marked and there are loss of appetite, nausea and vomiting, and, as the disease progresses, rapid loss of flesh' (Sir William Osler, 1892).

The occurrence of sepsis and multiple organ failure in certain patients in critical care units has been recognized as a syndrome during the last decade (Baue, 1975; Pine *et al.*, 1983). We have noted that neuropathy may be a complication which, because the syndrome has been called critical illness (Shoemaker, 1983), we have

previously termed 'critically ill polyneuropathy' (Bolton *et al.*, 1984). It has proven to be a major cause of difficulty in weaning patients from the ventilator as the critical illness comes under control (Bolton *et al.*, 1983). The clinical signs are often equivocal and electrophysiological investigations have been necessary to establish a diagnosis (Bolton *et al.*, 1983, 1984; Bolton, 1987). By this means, it has become evident that the polyneuropathy has a surprisingly high incidence, occurring in at least 50% of patients who have been septic for longer than two weeks (Witt *et al.*, 1985).

The precise cause remains obscure. The finding of a primary axonal degeneration of motor and sensory fibres, without inflammatory change, and the relatively normal cerebrospinal fluid, distinguish the neuropathy from the Guillain-Barré syndrome in most cases (Bolton *et al.*, 1986). Other causes to be considered include toxins, drugs, particularly antibiotics, and nutritional deficiency. We have now reviewed our clinical, electrophysiological and pathological experience with 19 cases encountered between 1977 and 1983, and analysed the data statistically. Preliminary results have been published (Zochodne *et al.*, 1985a, b).

## PATIENTS AND METHODS

### *Patients*

During a seven-year period, polyneuropathy was identified in 19 patients in the critical care unit, 17 by electrophysiological and 2 by postmortem studies. They had been admitted to the unit (17 at Victoria Hospital, 1 each at University and St Joseph's Hospitals in London, Ontario) with life-threatening disorders requiring intubation and other supportive measures, but without a primary neuromuscular disorder. They comprised 10 females and 9 males of mean age 64 (19–81) years. 'Failure to wean', the development of hypercarbia with reductions in intermittent mandatory ventilation frequency, prompted referral by the attending physicians 32 (6–87) days following intubation. During this interval all 19 patients developed sepsis, defined as septicaemia or localized infection with systemic effects, and multiorgan failure (Schumer, 1986; Pine *et al.*, 1983).

### *Electrophysiological Studies*

At an interval of 32 (6–87) days from admission to the unit, nerve conduction studies of median nerve motor and sensory fibres, peroneal nerve motor fibres and sural nerve sensory fibres were performed using surface stimulating and recording electrodes, according to standard techniques. Near nerve recordings of the sural nerve at the ankle were obtained by averaging 64 responses if a surface response had been absent. The sensory studies were antidromic in 15 and orthodromic in 2 patients. The phrenic nerve was stimulated at the thoracic inlet and the response recorded over the diaphragm (Markand *et al.*, 1984). Neuromuscular transmission was assessed by repetitive 3 and 20 Hz stimulation of median and ulnar nerves with recording from thenar and hypothenar muscles, respectively. Concentric needle electrode recordings were obtained routinely from deltoid, first dorsal interosseus, quadriceps, tibialis anterior, gastrocnemius and chest wall muscles, and additional muscles in some patients. Abnormal activity in resting muscle was graded as: +1, trains of positive waves or fibrillation potentials in at least two areas of the muscle; +2, trains in several areas; +3, trains in all areas; +4, numerous trains in all areas of the muscle. When possible, serial EMG and nerve conduction studies were performed at monthly intervals.

### *Analytical Methods*

The electrophysiological results were compared with 17 age and sex-matched control subjects and the results expressed as a percentage of the controls (figs 1, 2). On the basis of clinical and electrophysiological features, two groups were identified (1) mild polyneuropathy (8 patients) with mild electrophysiological changes (reductions of below two SDs in the amplitude of compound action potentials from either muscle or sensory nerve and abnormal spontaneous activity in muscles of at least two limbs) and absent or equivocal clinical signs of neuropathy; and (2) severe polyneuropathy (9 patients) with moderate or severe electrophysiological abnormalities with severe weakness and impairment of tendon reflexes. The amplitude of the compound muscle and sensory nerve action potentials were lower and the grade of abnormal spontaneous activity on EMG was higher, reflecting the greater severity of axonal degeneration in the severe compared with the mild polyneuropathy group (fig. 2).

Data that had been recorded on the hospital case records at various times for all patients were entered on a comprehensive protocol for later computer storage and analysis: clinical diagnoses, operative procedures, drug administration, infecting organisms, supplemented nutrition, serum and RBC folic acid, serum vitamin B<sub>12</sub>, urinary screen for porphobilinogen, serum aminoglycoside levels, arterial blood gases and lactate levels, blood lymphocyte count, heavy metal studies (lead, zinc and arsenic), episodes of hypotension, episodes of hypophosphataemia, CSF studies, EEG results and CT head scan findings.

The following biochemical studies that had been recorded in the case record (1) at admission to the critical care unit and (2) at the time the electrophysiological diagnosis of polyneuropathy was first made (events before this time were termed 'prediagnosis') were also entered on the protocol: serum creatine kinase, magnesium, urea, creatinine (including creatinine clearance and 4-hr urinary creatine excretion studies), bilirubin, alanine-leucine transaminase, lactic dehydrogenase, alkaline phosphatase, glucose, albumin and amylase levels. The mean of the various measurements of each biochemical value was calculated at the time of admission to the unit and later, at the time of diagnosis of polyneuropathy, for the 9 severe and the 8 mild polyneuropathy patients. These mean values and their change over the interval were compared between the two polyneuropathy groups.

The median levels of arterial pO<sub>2</sub>, pCO<sub>2</sub>, pH, HCO<sub>3</sub> and lactate from multiple daily determinations were tabulated for each day between intubation and diagnosis; mean prediagnosis levels were then calculated for each polyneuropathy group for comparison. A number of other factors were also examined: age, sex, mortality, duration of ventilation, exposure to hypotension, and both the amount (number of days) and intensity (proportion of days) of supplementary nutrition (total parenteral nutrition, TPN, and total enteral nutrition, TEN) before diagnosis and during improvement or worsening of the polyneuropathy. The exposure to hypotension was estimated as the number of hours of systolic blood pressure less than 90 mmHg requiring treatment before polyneuropathy diagnosis.

Statistical methods employed included mean estimates, independent and paired Student's *t* test, Fisher's exact  $\chi^2$  test, and Wilcoxon's rank sum test.

### *Neuropathological Studies*

Postmortem examinations were performed on 8 of the 19 patients. Following our initial analysis, we studied 1 further patient with polyneuropathy at autopsy. In addition, a premortem fascicular biopsy of superficial and deep peroneal nerves was obtained in 1 patient and another had a sural nerve biopsy. Samples of brain, spinal cord, peripheral nerve, and muscle were obtained at autopsy and fixed in 10% formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin, by Bodian's method for axons and by solochrome R for myelin. Selected portions of peripheral nerves were fixed in 2.5% cacodylate-buffered glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated and embedded in epon. Sections were stained with toluidine blue and viewed with the light microscope. Thin sections were stained with uranyl acetate and lead citrate and examined with

a Phillips 410 electron microscope. In 4 patients, individual nerve fibres from several nerves were teased and classified according to Dyck *et al.* (1984).

## RESULTS

### *Critical Illness*

Patients were intubated and transferred to the critical care unit following evaluation in the emergency room, or in the postoperative period, at a mean interval of 4 (0–24) days following admission to hospital. A variety of disorders precipitated placement in the critical care unit, including open heart or other major surgery, multiple trauma, acute exacerbation of chronic pulmonary disease and myocardial infarction. Although several patients were admitted to the unit with sepsis and its complications, a syndrome of multiple organ failure (Table 1) complicating sepsis most often developed later while patients were already being managed in the critical care unit. Acute respiratory failure in 15 patients was due to chronic airways limitation in 7, pneumonia in 6 and the 'adult respiratory distress syndrome' in 4 patients. Cardiac disease in 13 patients comprised coronary artery disease in 10, congestive failure in 3 and valvulopathy in 3. Hepatic dysfunction in 9 patients consisted of liver enzyme elevation or elevated serum bilirubin levels.

TABLE 1. DISTRIBUTION OF ORGAN DYSFUNCTION AND SOURCES OF SEPSIS IN 19 POLYNEUROPATHY PATIENTS

|                   | <i>No. of patients</i> | <i>Percentage frequency</i> |
|-------------------|------------------------|-----------------------------|
| Organ dysfunction |                        |                             |
| Pulmonary         | 15                     | 79                          |
| Cardiac           | 13                     | 68                          |
| Hepatic           | 9                      | 47                          |
| Renal             | 3                      | 16                          |
| Other             | 16                     |                             |
| Sepsis            |                        |                             |
| Sputum            | 12                     | 89                          |
| Urine             | 15                     | 79                          |
| Blood             | 9                      | 47                          |
| Other             | 12                     |                             |

Failure of the CNS was difficult to assess because the patients were intubated and often sedated. We suspected septic encephalopathy (Jackson *et al.*, 1985) on the basis of drowsiness or apparent confusion in all 19 patients. A more obvious diffuse encephalopathy was present in 4 patients. In addition, 2 patients had cerebral infarction, 2 had brainstem infarcts and 1 had craniocerebral trauma. EEG studies were abnormal in 11 and normal in 2 patients; 6 patients had an abnormal EEG but normal CT head scan.

A history of premorbid polyneuropathy was not present in 3 patients with

mild renal failure, 3 patients with mild diabetes mellitus and single patients with alcoholism, hypothyroidism, carcinoma and rheumatoid arthritis.

All patients had evidence of sepsis. Blood cultures were positive in 9, while sputum, urine or other cultures were judged positive and significant in all remaining patients except 1 before the diagnosis of polyneuropathy. In 1 patient, pulmonary sepsis became evident at the time of diagnosis. Routes of infection included surgical wounds, central lines, chest tubes and urinary catheters. All patients were given some form of intravenous antibiotic therapy for 24 (3–61) days before the diagnosis of polyneuropathy. Multiple concurrent and sequential infections often preceded and followed the diagnosis of polyneuropathy. The following organisms were grown on blood culture (prediagnosis): *Staphylococcus epidermidis* (excluding contaminants), 5 patients; *Enterococcus*, 2 patients; *E. Coli*, 2 patients; *Serratia marcescens*, 2 patients; and *Staphylococcus aureus*, *Acinetobacter*, diphtheroids, *Enterobacter*, *Klebsiella*, *Pneumococcus*, 1 patient each. Five patients had two or more distinct episodes of bacteraemia before polyneuropathy was diagnosed. Viral titres measured in 11 patients were elevated for cytomegalovirus in 3 patients, herpes simplex in 3 patients, and influenza A and mycoplasma pneumoniae in 1 patient each.

Of 19 patients, 11 died (58% mortality rate). This included 5 of 9 severe polyneuropathy patients, 4 of 8 mild polyneuropathy patients and the 2 patients in whom the diagnosis was established at autopsy. Although polyneuropathy was not a direct cause of death, other complications of sepsis and multiple organ failure were (see below).

### *The Features of Polyneuropathy*

The symptoms of polyneuropathy were often difficult to elicit because of sedation, encephalopathy and intubation. Only 2 patients were able to report sensory symptoms—limb paraesthesiae in 1 and jabbing foot pain in another. The multiple lines, drains, monitors and dressings required for intensive support limited the neurological examination. The only cranial nerve involvement was mild upper and lower facial weakness in 3 patients. Limb weakness was usually symmetric and worse distally (Table 2). Three patients had a severe, flaccid, areflexic quadriparesis not attributable to CNS disease. Distal wasting was difficult to assess because of oedema, but was observed at the time of diagnosis in 3 patients and in 2 others at follow-up. Distal impairment to pain, temperature and vibration perception was present in 4 patients but could not be determined reliably in the remainder. The tendon reflexes were reduced or absent in 15 patients. The autonomic nervous system was not tested.

The diagnosis of 'failure to wean' was made when, despite partial resolution of the critical illness, the patient could not tolerate a reduction in the frequency of mandatory mechanical ventilation. Patients developed rapid and shallow respirations followed by hypercarbia. In 2 patients we observed paradoxical respiratory movements (thoracic indrawing and abdominal excursion with

TABLE 2. FREQUENCY OF  
CLINICAL SIGNS OF  
POLYNEUROPATHY

| <i>Clinical sign</i> | <i>No. of patients</i> |
|----------------------|------------------------|
| Motor                |                        |
| Weakness             |                        |
| None                 | 4                      |
| Mild                 | 3                      |
| Moderate             | 3                      |
| Severe               | 5                      |
| Unknown              | 4                      |
| Wasting              | 4                      |
| Fasciculations       | 2                      |
| Sensory loss         |                        |
| Pain temperature     | 4                      |
| Vibration            | 3                      |
| Position             | 1                      |
| Unknown              | 16                     |
| Tendon reflexes      |                        |
| Normal               | 4                      |
| Reduced              | 9                      |
| Absent               | 6                      |

inspiration), suggesting greater intercostal than diaphragmatic weakness. Critical illness precluded detailed spirometric evaluation. The mean total duration of ventilation until death or extubation was 67 (10–134) days. This figure was 74 days for patients with severe and 62 days for those with mild polyneuropathy (difference not significant).

All 8 survivors had later resolution of the signs of polyneuropathy as the critical illness subsided. In 4 patients the polyneuropathy began to improve but death supervened as the result of their systemic illness. Although an improvement in limb strength was the first clinical sign of recovery, reappearance of tendon reflexes was the most objective sign. In severe polyneuropathy, tendon reflexes reappeared one to three months after successful weaning. Improvement often occurred first in upper limbs and proximal lower limbs, followed by the respiratory system, and later the distal lower limbs.

### *Electrophysiological Studies*

The nerve conduction and needle EMG results in the 17 patients were expressed as a percentage of control values (Table 3). The distal latencies, conduction velocities and F wave latencies were relatively preserved (fig. 1). Compound muscle

|                       |        |                         |
|-----------------------|--------|-------------------------|
| Conduction velocity   |        |                         |
| Median motor          | 54.8 ± | 3.1 m · s <sup>-1</sup> |
| Median sensory        | 56.0 ± | 5.6 m · s <sup>-1</sup> |
| Peroneal motor        | 46.0 ± | 4.8 m · s <sup>-1</sup> |
| Sural sensory         | 45.9 ± | 6.0 m · s <sup>-1</sup> |
| F wave latency        |        |                         |
| Median                | 28.3 ± | 1.9 ms                  |
| Peroneal              | 51.9 ± | 3.8 ms                  |
| Distal latency        |        |                         |
| Median motor          | 3.6 ±  | 0.4 ms                  |
| Median sensory        | 2.5 ±  | 0.2 ms                  |
| Amplitude             |        |                         |
| Thenar muscle         | 10.1 ± | 2.6 mV                  |
| Digital nerve: female | 21.4 ± | 9.2 μV                  |
| : male                | 19.0 ± | 10.6 μV                 |
| EDB muscle            | 4.3 ±  | 2.0 mV                  |
| Sural nerve           | 11.2 ± | 4.9 μV                  |
| Temperature           |        |                         |
| Hand                  | 31.8 ± | 1.7 °C                  |
| Foot                  | 29.5 ± | 1.1 °C                  |

Needle EMG disclosed fibrillation potentials and positive sharp waves, and occasional myotonic or complex repetitive discharges. This activity was not confined to a particular nerve or root distribution and involved both distal and proximal muscles, but varied in amount among muscle groups in a multifocal manner. Voluntary units were diminished in number, either due to denervation or poor recruitment, the remaining units being normal or small in size, and often polyphasic. EMG studies of the facial muscles in 7 patients revealed mild denervation in 3.

Phrenic nerve conduction studies were normal in 6 patients but in 2 with severe polyneuropathy the compound muscle action potentials from the diaphragm were absent bilaterally. In 13 patients, the external oblique and external intercostal muscles had evidence of denervation, with abnormal spontaneous activity or loss of rhythmic recruitment with breathing.

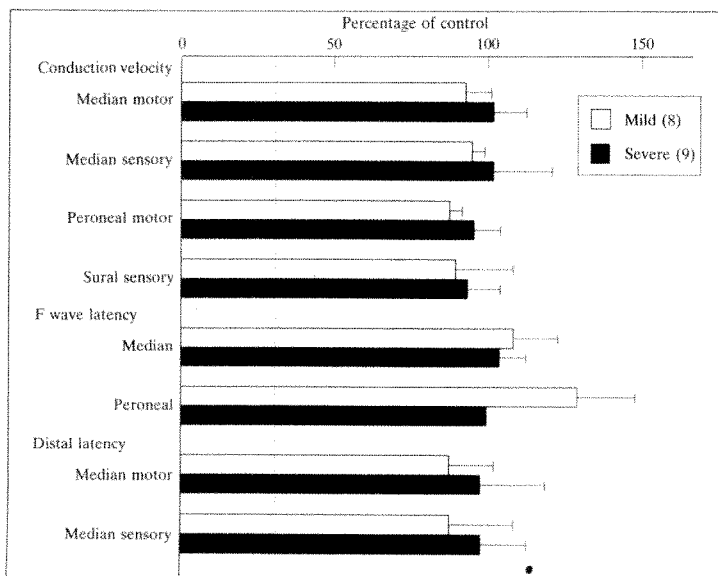


FIG. 1. Electrophysiological studies in 17 patients who had critical illness polyneuropathy. The values are plotted as a percentage, mean  $\pm$  SD, of control values. The patients were divided into two groups on the basis of clinical and electrophysiological observations (*see Methods*): 8 with mild, and 9 with severe polyneuropathy. These values reflect the speed of impulse conduction and are relatively normal, as expected in a primary axonal degeneration of nerves. Neither group differed significantly from each other, or from the control group.

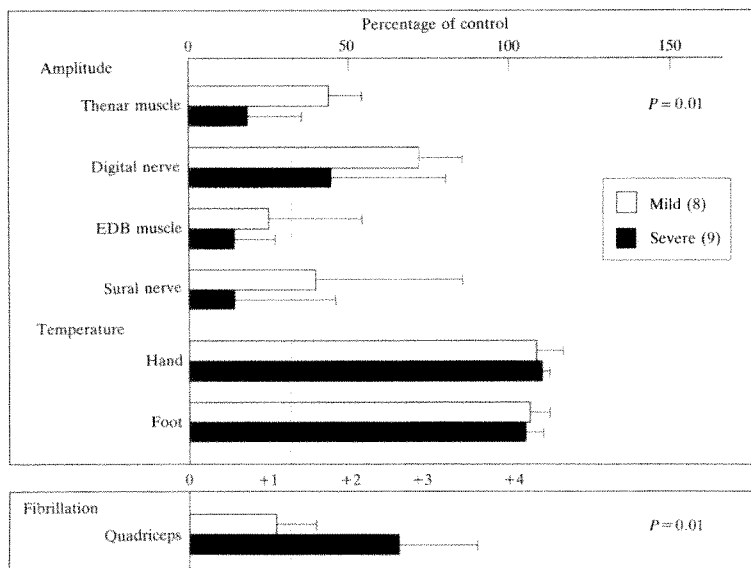


FIG. 2. Further electrophysiological studies. All patients had considerably depressed compound muscle and sensory nerve action potential amplitudes, elevated limb temperature and abnormal spontaneous activity in muscle. These findings, and those depicted in fig. 1, are consistent with an axonal degeneration of motor and sensory fibres and denervation of muscle. The *P* values in the figure indicate where results in the severe and mild polyneuropathy groups were significantly different. EDB = extensor digitorum brevis.



In 11 patients, serial studies demonstrated recovery. Previously absent compound muscle and sensory nerve action potentials reappeared; amplitudes gradually returned to the normal range. Abnormal spontaneous activity disappeared, first in proximal and then in distal muscles. The voluntary motor units were polyphasic, indicative of reinnervation. This electrophysiological improvement accompanied return of tendon reflexes and successful weaning from the mechanical ventilator. In 2 patients, electrophysiological improvement predicted successful weaning one month later and eventual return of tendon reflexes. In 6 patients, serial studies first indicated improvement 2.5 (1–5) months following the initial study. Studies became normal 6 months to 1 year after diagnosis, even in patients with severe polyneuropathy.

### *Other Studies*

The CSF was examined in 11 patients: 3 had mildly elevated protein levels (less than 0.8 g/l) and 1 had 12 mononuclear cells/ $\mu\text{l}^3$  initially, and then only 1 white cell/ $\text{mm}^3$  one month later. The remaining patients had normal CSF. In 3 patients, examination of the CSF for oligoclonal IgG banding was negative. The following studies were also normal: urine for porphobilinogen (10 patients), serum folate (9 patients), RBC folate (7 patients), serum vitamin B<sub>12</sub> (10 patients), serum lead (2 patients), urine lead (1 patient), serum zinc (2 patients) and blood arsenic (1 patient). One patient had low serum folate levels.

### *Case Reports*

*Case 1 (severe polyneuropathy).* A 65-year-old female was admitted to the emergency department with multilobular pneumonia, confusion and hypotension. There was a previous history of hypertension and chronic obstructive pulmonary disease. Shortly after arrival, she suffered a respiratory arrest, requiring intubation and transfer to the critical care unit. Sputum and blood cultures grew *Streptococcus pneumoniae*. Over the next several days, although she was treated with penicillin G, tobramycin and cloxacillin she developed the adult respiratory distress syndrome. Initial neurological examination shortly after admission disclosed encephalopathy and extensor plantar responses but normal motor power and tendon reflexes. A CT head scan and CSF were normal. An EEG revealed mild generalized suppression. Over the next several weeks, she developed elevated levels of serum amylase and hepatic enzymes, a pneumothorax, a bronchopleural fistula and phlebitis. She required several courses of aminoglycosides for recurrent infections and had mildly elevated trough levels of serum tobramycin.

Two months following admission, she was still unable to breathe independently but was able to complain of stabbing foot pain. She had developed heavy pigmentation, deafness (due to aminoglycosides), weakness in all limbs and areflexia. Median and common peroneal nerve conduction studies revealed normal conduction velocities and distal latencies but reduced amplitudes of compound muscle and sensory nerve action potentials. The sural compound action potential was absent. The diaphragm potential was absent on bilateral phrenic nerve stimulation. Needle EMG showed numerous trains of fibrillation potentials and positive sharp waves (+4) in quadriceps, medial gastrocnemius, first dorsal interosseus, right deltoid and right chest wall muscles. Studies of adrenal function were normal and the pigmentation was postulated to be secondary to elevated levels of catecholamines.

One month later, muscle strength had improved and pigmentation lessened, but she remained deaf.

arreflexic and ventilator-dependent. Compound muscle action potential amplitudes had improved. Sural nerve potentials had returned and needle EMG revealed less abnormal spontaneous activity in various muscles.

Four months after admission, she was weaned from the ventilator. Tendon reflexes had returned in the arms. Compound muscle and sensory nerve action potentials had improved further and spontaneous activity had subsided with the appearance of polyphasic voluntary motor units. Six months following admission, she was discharged ambulatory, with a mild right foot drop and absent ankle jerks.

At a two-year follow-up examination, she had normal skin pigmentation, was moderately deaf, had mildly weak dorsiflexion of the right foot and absent ankle jerks. Nerve conduction studies were normal.

*Case 2 (mild polyneuropathy).* A 74-year-old female was admitted to hospital with acute pancreatitis culminating a six-month history of postcholecystectomy abdominal pain, anorexia and weight loss. There was a previous history of ischaemic heart disease. Two days following admission she developed acute bradycardia with heart block. A temporary pacemaker was inserted. She was admitted to the critical care unit and was treated for hypotension. Hyperglycaemia, pulmonary oedema and fluctuating drowsiness developed over the next few days. On the nineteenth hospital day, she was taken to the operating room where laparotomy was performed and an infected pancreatic pseudocyst was drained. Cultures from the pancreatic fluid and blood grew *Klebsiella oxytoca* and *E. coli*. Gentamycin and cefamandole were administered.

On the thirtieth hospital day, she appeared alert but could not follow simple commands. Motor examination and the tendon reflexes were normal but the plantar responses were extensor. The CSF was normal. Nerve conduction studies were within normal limits but needle EMG disclosed fibrillation potentials and positive sharp waves in quadriceps (+2), gastrocnemius (+2), the first dorsal interosseus (+3), and the fifth intercostal muscles (+1). Voluntary motor unit potentials were reduced in number and fired rapidly. Stimulation of the left ulnar nerve at 3 and 20 Hz with recording over hypothenar muscle did not disclose a neuromuscular transmission defect. She was extubated at six weeks.

Examination at eight weeks revealed mild tremulousness and confusion with mild weakness and wasting of all limbs, especially distally. The tendon reflexes were absent at the ankles, reduced at the knees and the plantar responses were extensor. Sensory examination was normal, except for mildly reduced vibration perception in the toes. She was discharged on day 51. Follow-up at twelve weeks disclosed a normal mental status, mild distal limb wasting and weakness, an absent left ankle jerk and reduced vibration sensation in the toes. At 18 weeks mild clinical and electrophysiological signs of polyneuropathy remained.

#### *Analysis of Case Records*

*Drug administration.* A large number of drugs were given. The most frequently used were: KCl boluses (18 patients), morphine (17), diazepam (17), frusemide (17), aminophylline (16), aluminium hydroxide (16), acetaminophen (14), cimetidine (13) and hydralazine (10). Hydralazine was used when required, infrequently for acute hypertension. The frequency of potassium chloride and frusemide boluses administration did not correlate with the severity of the polyneuropathy. Amino glycosides were given before the diagnosis of polyneuropathy in 4 patients with mild, and 6 with severe polyneuropathy; 7 patients did not receive aminoglycosides before diagnosis. Mean peak and trough aminoglycoside levels did not correlate with polyneuropathy severity and peak levels were within the recommended therapeutic range. Trough levels were slightly above the therapeutic range but only 1 patient developed ototoxicity (Case 1).

*Biochemical studies.* Elevations of serum creatine kinase were sporadic and often due to myocardial necrosis. Serum creatinine and creatinine excretion fell between admission and diagnosis in all patient groups. The mean serum creatinine in both groups was  $141 \pm 53 \mu\text{mol/l}$  at admission and

$88 \pm 35 \mu\text{mol/l}$  at diagnosis (normal  $70\text{--}120 \mu\text{mol/l}$ ) ( $P < 0.05$ ). The serum glucose was higher in patients with severe neuropathy ( $10.3 \pm 2.8 \text{ mmol/l}$ ) than those with mild neuropathy ( $7.6 \pm 1.8 \text{ mmol/l}$ ) at diagnosis ( $P < 0.05$ ) but was similar on admission ( $9.7 \pm 4.2$  and  $11.2 \pm 8.0 \text{ mmol/l}$ ) (n.s.) (normal  $2.2\text{--}4.4 \text{ mmol/l}$ ). The serum albumin concentration was lower at diagnosis in severe polyneuropathy ( $27 \pm 4 \text{ g/l}$ ) than in mild polyneuropathy ( $32 \pm 2 \text{ g/l}$ ) ( $P < 0.05$ ), and there was a similar trend on admission (severe  $28 \pm 9$ ; mild  $33 \pm 5$ ;  $P = \text{n.s.}$ ) (normal  $35\text{--}50 \text{ g/l}$ ). The following mean serum levels were elevated at diagnosis in all patients: lactic dehydrogenase,  $416 \pm 259 \text{ U/l}$  (normal  $100\text{--}225$ ); alanine leucine transaminase,  $57 \pm 38 \text{ U/l}$  (normal  $7\text{--}40$ ); bilirubin,  $18.8 \pm 23.9 \mu\text{mol/l}$  (normal less than  $10.0$ ); amylase,  $172 \pm 126 \text{ U/l}$  (normal  $10\text{--}85$ ); urea,  $9.6 \pm 8.6 \text{ mmol/l}$  (normal  $3.5\text{--}7.0$ ). The mean creatinine clearance at diagnosis was  $0.80 \text{ ml/s}$  (normal  $1.25\text{--}2.25$ ).

Mean serum inorganic phosphate levels were within the normal range on both admission and at diagnosis. Transient episodes of mild hypophosphataemia occurred commonly but 4 patients with severe polyneuropathy did not have a fall in any of the daily serum inorganic phosphate levels drawn prior to diagnosis.

Mean arterial lactate levels did not differ between the polyneuropathy groups. The mean arterial lactate level in 14 patients in whom it was measured before diagnosis was  $1.6 \text{ mmol/l}$  (normal  $0.5\text{--}1.8$ ); 5 patients had mean levels greater than  $1.8$ , 4 of whom had positive blood or wound cultures. Transient elevations of lactate were common.

**Supplemented nutrition.** Before diagnosis, total parenteral nutrition (TPN) was given to 15 patients and total enteral nutrition (TEN) by nasogastric feeding tube to 13 patients. All patients had received either one or the other form of nutrition before diagnosis. The amount and intensity (proportion of time administered) of supplementation was similar in each polyneuropathy group. Patients received supplemented nutrition for an average of 75% of the time between admission and diagnosis of polyneuropathy. Supplementation did not vary significantly between diagnosis and reassessment in patients who improved, deteriorated or stayed the same. TPN solutions provided electrolytes including phosphate, manganese chloride, copper chloride, chromium nitrate, potassium iodide, zinc sulphate. Additional vitamin supplementation in all solutions included thiamine, riboflavin, nicotinamide, biotin, pyridoxine, pantothenic acid, ascorbic acid, vitamin A, vitamin D, vitamin E, vitamin K, folic acid, and vitamin B<sub>12</sub>. Iron and selenium were provided in some solutions. Aminoacids and lipid emulsions were also included. Fat emulsions were soya bean oil. (Most patients were given Nutralipid, Pharmacia, with linoleic acid (50%), oleic acid (26.5%), palmitic acid (10.5%), linolenic acid (8.5%) and stearic acid (3.5%); Intralipid, Cutter, was also given.) In 1 patient, the emulsion contained safflower oil (Liposyn, Abbott). Enteral nutrition was usually provided as Ensure (Ross), or Vivonex (Norwich-Eaton).

**Other factors.** The following results did not correlate with the severity of the polyneuropathy: age, sex, infecting organisms, viral titres, exposure to hypotension or arterial studies of  $\text{pO}_2$ ,  $\text{pCO}_2$ , pH, and  $\text{HCO}_3^-$ .

TABLE 4. SUMMARY OF AUTOPSY RESULTS

| Case        | Peripheral nerve                                                                         | Muscle                                                                                     | Other                                                                               | General autopsy                                                                                                      |
|-------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 1 65 yrs, M | Axonal degeneration<br>Superficial peroneal +<br>Deep peroneal +<br>Phrenic +<br>Vagus + | Grouped fibre atrophy<br>Quadriceps + + +<br>Triceps, peroneus longus + +<br>Diaphragm + + |                                                                                     | Multifocal pneumonia<br>Emphysema, bronchitis<br>Atherosclerosis<br>Adrenal necrosis                                 |
| 2 59 yrs, F | Axonal degeneration<br>Superficial peroneal +<br>Deep peroneal +<br>Dorsal roots +       | Grouped fibre atrophy<br>Peroneus longus + + +<br>Extensor hallucis longus                 | Chromatolysis of<br>anterior horn<br>cells<br>Loss of dorsal root<br>ganglion cells | Bronchopneumonia<br>Lung abscess<br>Pulmonary oedema<br>Cardiomegaly<br>Atherosclerosis<br>Mastitis<br>Brain purpura |

TABLE 4. SUMMARY OF AUTOPSY RESULTS *Contd.*

| <i>Case</i> | <i>Peripheral nerve</i>                                                                                                                                                                                      | <i>Muscle</i>                                                                                                                                                             | <i>Other</i>                                                                        | <i>General autopsy</i>                                                                                                                             |
|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| 3 76 yrs, M | Axonal degeneration<br>Superficial peroneal +<br>Deep peroneal +<br>Sura +<br>Large fibre loss                                                                                                               | Grouped fibre atrophy<br>Tibialis anterior + +<br>Diaphragm +<br>Single fibre necrosis<br>Targetoid changes                                                               |                                                                                     | Pulmonary infarct<br>Myocardial infarct<br>Ischaemic<br>encephalomyelopathy<br>Atherosclerosis<br>L ventricular<br>hypertrophy                     |
| 4 61 yrs, M | Axonal degeneration<br>Superficial peroneal + + +<br>Deep peroneal + + +                                                                                                                                     | Grouped fibre atrophy<br>Psoas, pectoralis major +<br>Intercostal, peroneus brevis +<br>Necrosis<br>Tibialis anterior<br>Peroneus brevis                                  | Chromatolysis of<br>anterior horn<br>cells                                          | Pulmonary infarct<br>Myocardial infarct<br>Septal rupture<br>Cerebral infarcts<br>Atherosclerosis                                                  |
| 5 29 yrs, M | Axonal degeneration<br>Superficial peroneal + + +<br>Deep peroneal + + +<br>Normal<br>Dorsal root<br>Ventral root                                                                                            | Grouped fibre atrophy<br>Quadriceps + + +<br>Gastrocnemius + + +<br>Tibialis anterior + + +<br>Peroneus longus + + +<br>Deltoid + +<br>Psoas, paraspinal<br>intercostal + |                                                                                     | Pulmonary abscess<br>Bronchopulmonary<br>fistulae<br>Adult respiratory<br>distress syndrome<br>Craniocerebral trauma<br>Endocarditis               |
| 6 59 yrs, F | Axonal degeneration<br>Cauda equina +<br>Phrenic +                                                                                                                                                           | Grouped fibre atrophy<br>Psoas, pectoralis major +<br>Central nuclei<br>Pectoralis major<br>Targetoid changes<br>Diaphragm                                                | Loss of dorsal root<br>ganglion cells                                               | Pulmonary infarct<br>Emphysema, asthma<br>Pneumothorax<br>Haemothorax<br>Pseudomonas sepsis<br>Ischaemic<br>encephalopathy<br>Bowel perforation    |
| 7 74 yrs, M | Axonal degeneration<br>Superficial peroneal +<br>Phrenic +                                                                                                                                                   | Grouped fibre atrophy<br>Peroneus longus +<br>Diaphragm +<br>Intercostal +                                                                                                |                                                                                     | Pulmonary abscess<br>Pneumonia<br>Myocarditis and<br>cardiac failure<br>Peptic ulceration<br>Ischaemic<br>encephalopathy                           |
| 8 67 yrs, F | Axonal degeneration<br>Superficial peroneal + + +<br><br>Myelin loss<br>Brachial plexus<br>Lumbosacral plexus<br>Femoral                                                                                     | Grouped fibre atrophy<br>Diaphragm + + +<br>Biceps, psoas +<br><br>Deltoid +                                                                                              |                                                                                     | Emphysema<br>Acute haemorrhage<br>into coronary artery<br>plaque<br>Atherosclerosis                                                                |
| 9 58 yrs, M | Axonal degeneration<br>Superficial peroneal + + +<br>Deep peroneal + + +<br>Intramuscular twig + +<br>Intercostal +<br>Lumbar trunk +<br>Cauda equina +<br>Large fibre loss<br>Sural + +<br>Cauda equina + + | Grouped fibre atrophy<br>Tibialis anterior +<br>Intercostal +<br>Single fibre necrosis<br>Tibialis anterior<br>Intercostal                                                | Chromatolysis of<br>anterior horn<br>cells<br>Loss of dorsal root<br>ganglion cells | Pneumonia<br>Adult respiratory<br>distress syndrome<br>Lung abscess<br>Multiple bony fractures<br>Cardiomegaly<br>Ischaemic<br>encephalomyelopathy |

+ = mild; + + = moderate; + + + = severe. F = female; M = male.

### Pathology

Autopsy was performed in 8 of the 11 patients who died. Following completion of the above analysis, we studied 1 further patient whose autopsy results are included (Case 9) with the others in Table 4. The results have been previously published in abstract form (Zochodne *et al.*, 1985b).

Fibre loss and degeneration were the most frequent abnormalities identified in peripheral nerve (figs 3, 4). Distal segments had the most severe involvement. Significant inflammation was not

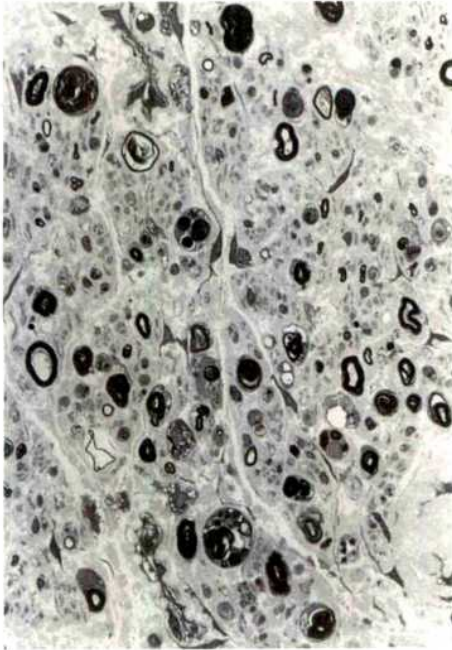


FIG. 3. Case 5. Transverse section of the superficial peroneal nerve showing severe axonal degeneration and loss of myelinated fibres. Toluidine blue,  $\times 773$ .



FIG. 4. Case 4. Longitudinal section of the deep peroneal nerve demonstrating axonal degeneration and loss of myelinated fibres. Toluidine blue,  $\times 778$ .

observed. In teased fibre preparations, significant segmental demyelination and remyelination were not seen, and the chief, presumably primary, abnormality was axonal degeneration (Table 5). Additional features were central chromatolysis of anterior horn cells (fig. 5) and moderate loss of dorsal root ganglion cells. There was evidence of both acute and chronic denervation atrophy in distal and proximal muscle groups. Muscle fibre necrosis suggested a complicating myopathy in 4

TABLE 5. RESULTS OF TEASED FIBRE ANALYSIS IN 4 PATIENTS

| Case | Nerve                | A,B<br>(%) | C<br>(%) | D<br>(%) | E<br>(%) | F<br>(%) | N   |
|------|----------------------|------------|----------|----------|----------|----------|-----|
| 1    | Superficial peroneal | 83.7       |          |          | 4.5      | 11.8     | 110 |
| 2    | Superficial peroneal | 75         |          |          | 22.1     | 2.9      | 140 |
| 5    | Superficial peroneal | 4.9        | 0.9      |          | 94.4     |          | 144 |
| 9    | Deep peroneal        | 20         |          |          | 80       |          | 81  |

A,B = normal; C = paranodal demyelination; D = segmental demyelination; E = axonal degeneration; F = segmental remyelination; N = number of individual nerve fibres analysed.



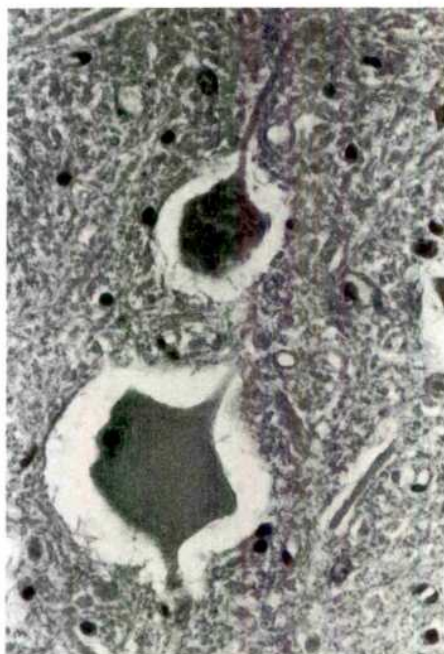


FIG. 5. *Case 9.* Transverse section of the lumbar cord showing central chromatolysis in one of the two cells. Haematoxylin and eosin,  $\times 458$ .

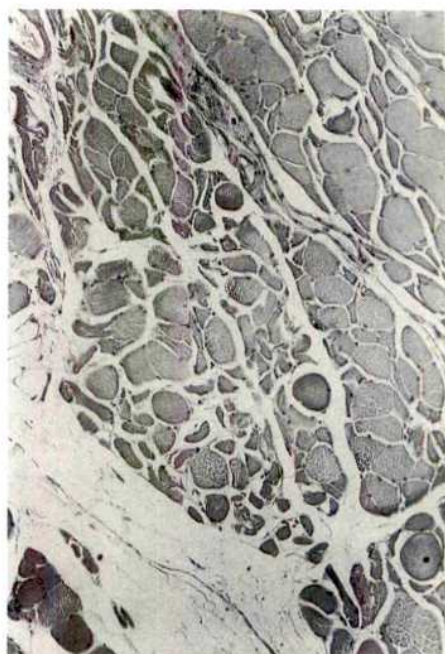


FIG. 6. *Case 4.* Transverse section of intercostal muscle showing the variation in muscle fibres size with scattered and grouped atrophic fibres signifying denervation atrophy. Haematoxylin and eosin,  $\times 195$ .

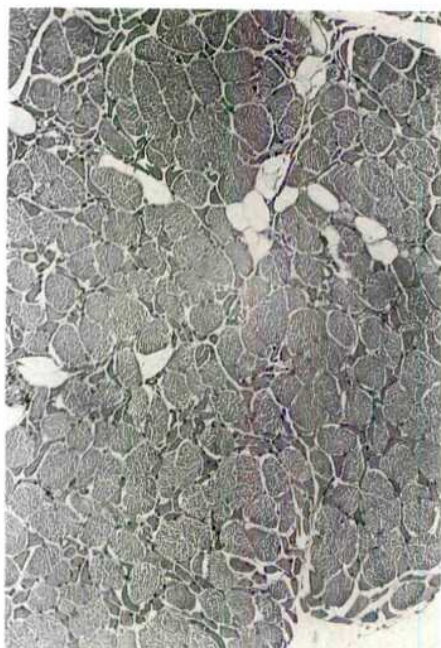


FIG. 7. *Case 4.* Transverse section of iliopsoas muscle showing scattered and grouped atrophic fibres consistent with denervation atrophy. Haematoxylin and eosin,  $\times 195$ .

patients (serum CK levels were elevated). Phrenic and intercostal nerves demonstrated mild axonal degeneration. In 8 patients, the respiratory muscles were examined and denervation atrophy was observed (fig 6).

Examination of the CNS disclosed ischaemic encephalopathy (4 patients), small infarcts (1 patient), craniocerebral trauma (1 patient), brain purpura (1 patient) or no change despite clinical encephalopathy (1 patient). Wernicke's disease was not observed. General autopsy results frequently included evidence of pulmonary sepsis and thromboembolic disease (Table 4).

## DISCUSSION

### *The Syndrome of Sepsis and Multiple Organ Failure (Critical Illness)*

A syndrome of sepsis and multiple organ failure or critical illness is being recognized with increasing frequency in intensive or critical care units. The incidence depends upon the type of patient admitted to the unit concerned. Our unit admits approximately 1,000 patients per year (excluding routine postoperative admissions) following major operations, overwhelming injury or severe medical illness. Approximately 5% of these patients develop the syndrome, of whom 60% die. However, because many require prolonged convalescence or linger for weeks before death, the prevalence at any one time may be 20% or higher.

Although many aspects of the syndrome remain obscure, it has been actively investigated by a number of disciplines (Schumer, 1986). Several conditions appear to predispose patients, particularly elderly ones, to the development of critical illness. These include multiple trauma, major surgery or severe medical illness. Such patients are susceptible to infection because they have cutaneous anergy, impaired neutrophil chemotaxis and adherence, reduced lymphocyte rosetting and depressed fibronectin, all of which may recover with successful surgical or medical treatment (Meakins *et al.*, 1977, 1979; Meakins, 1986; Richards *et al.*, 1983). Infection complicating a severe primary event is an important, but not invariable, part of the syndrome. It is particularly likely to arise from invasive procedures such as intubation and intravenous lines. However, in a few instances, multiple organ failure may occur without the intervening effects of sepsis and arise simply as a result of the severe primary illness or injury. These series of events may take place over a matter of days, weeks or months. All major organ systems may eventually be affected.

Many of the clinical (Rackow, 1986) and pathological features (Coalson, 1986) of critical illness have been described. The fundamental mechanisms by which multiple organ systems are involved are complex. These mechanisms can be divided into several broad categories.

Sepsis, the dominant component of the syndrome, is defined as the systemic response to dividing and invading micro-organisms of all types: Gram negative and Gram positive bacteria, fungi and viruses (Ayres, 1986). Their presence stimulates activity by the macrophage system, granular leucocytes and platelets. These cells, particularly macrophages, elaborate proteins previously known as endogenous

pyrogens, now termed monokines or interleukin-1 which are important in mediating the septic syndrome. Their presence induces alterations of temperature, immunity, metabolism and endocrine function. The results may include muscle proteolysis, gluconeogenesis and lipid catabolism, and increased levels of insulin and glucagon. Vasoconstriction and increased blood vessel permeability occur through the action of eicosanoids (Lefer, 1985).

Profound haemodynamic changes occur in critical illness. In the early stages of sepsis there is a generalized vasodilatation with increased cardiac output. Because of local factors, vascular resistance falls and hypotension ensues if intravenous fluids are not given. This may be a result of impaired cellular oxygen extraction, leading to a rise both in arterial and venous blood oxygen. However, a stage of decompensated sepsis later occurs, in which there is both decreased peripheral blood flow and reduced oxygen extraction from tissues. Anaerobic metabolism becomes necessary in muscle, causing a shift of pyruvate to lactate and metabolic acidosis. Cardiac output falls and shock supervenes (MacLean *et al.*, 1967). The shock may be successfully treated, only to recur, so that these patients often undergo repeated episodes of septic shock.

Complex metabolic changes develop. The mediators of the septic syndrome induce a catabolic state, presumably to meet the needs of increased energy requirements. Branch chain amino acids are released into the circulation and act as a substrate during this process (Cerra *et al.*, 1983; Ayres, 1986). Levels of glucagon, adrenaline and cortisol rise. Uncontrolled gluconeogenesis results in hyperglycaemia despite increased levels of insulin (Gump *et al.*, 1974; Clowes *et al.*, 1976). Either as a result of toxins from infecting organisms, the mediators of the septic syndrome, or possibly ischaemia due to decreased blood flow, there is eventual dysfunction of liver mitochondria, even though these mitochondria initially function normally. Translocase activity is impaired, resulting in a fall in ATP levels in liver cells, but not apparently in muscle (Clowes *et al.*, 1976; Chaudry *et al.*, 1979; Ohkawa *et al.*, 1983; Ayres, 1986).

The final stage of this process is the development of multiple organ failure. It involves all organs and organ systems, but the effects on the brain, lung, heart, kidney, liver and gastrointestinal tract are prominent.

### *Septic Encephalopathy*

Preliminary studies in our hospital indicate that encephalopathy, usually of a mild degree, occurs in many patients during the early stages of sepsis (Bolton and Young, 1986). However, once the stage of multiple organ dysfunction has been reached, all will have developed an encephalopathy, usually severe. It is characterized by a deepening level of unconsciousness and often by focal or multifocal seizures. Structural lesions have consisted of diffuse microabscess formation, central pontine myelinolysis, diffuse microhaemorrhages due to coagulation defects, and multiple cerebral infarctions. However, no lesions are present in some cases, suggesting that toxic and metabolic events are an important cause of the encephalo-



lopathy (Jackson *et al.*, 1985). These events are presumably related to the complex systemic effects of sepsis and multiple organ failure, as discussed above.

### *Critical Illness Polyneuropathy*

Polyneuropathy is a further manifestation of the syndrome of critical illness. Our 19 patients had a prolonged stay in the critical care unit (mean 68 days), with failure in at least two organ systems, and sepsis. Bacteraemia was documented in approximately half, a proportion observed by others (Meakins *et al.*, 1980). Arterial lactate levels, a measure of severity of the sepsis, were often elevated (Duff *et al.*, 1969; Weil and Afifi, 1970). The prominence of pulmonary and cardiac involvement and the elevated levels of hepatic enzymes, bilirubin, glucose and amylase are all features of the multiple organ failure syndrome. The low albumin levels and fall in creatinine suggest that protein breakdown and a decline in muscle mass accompanied the critical illness. The elevated skin temperatures (fig. 2) are also consistent with sepsis (Rackow, 1986). Our patients had a mortality rate of 58%, which approximates that reported by others (Pine *et al.*, 1983).

The difficulty in examining and studying critically ill patients may explain why this complication has only recently been recognized. Clinical symptoms are often impossible to obtain. The signs of limb weakness and loss of previously elicited tendon reflexes are not present in all patients, even those who are subsequently shown by electrophysiological studies to have a moderately severe polyneuropathy. Wasting may be difficult to detect when patients have generalized oedema, a manifestation of abnormal fluid extravasation and cell permeability in critical illness (Flear *et al.*, 1980). 'Failure to wean', an important early sign, is nonspecific. Finally, patients may not remember the symptoms of polyneuropathy because of encephalopathy (Jackson *et al.*, 1985).

Electrophysiological examination was the most important means of establishing the diagnosis in our patients. Studies were performed by transporting the patient to the EMG laboratory or by using a portable machine in the critical care unit. Low compound muscle and sensory nerve action potential amplitudes and widespread needle electromyographic signs of acute denervation of muscle (Brown, 1984) were characteristic findings. Elevated body skin temperatures encountered in our patients did not account for the magnitude of the electrophysiological changes (Bolton *et al.*, 1982). Voluntary motor unit activity was often absent, due to denervation or to failure of volitional recruitment because of encephalopathy. Intercostal muscle denervation and failure to evoke a diaphragmatic response on phrenic nerve stimulation indicated involvement of respiratory muscles. During recovery, compound muscle action potential amplitudes improved, spontaneous activity disappeared, and complex polyphasic voluntary motor unit potentials reappeared. In all patients who survived critical illness, clinical and electrophysiological recovery from polyneuropathy was almost complete.

The morphological features, in keeping with the electrophysiological features,

indicated primary axonal degeneration of motor and sensory fibres (Bolton *et al.*, 1979; Thomas, 1984). The resulting denervation atrophy was widespread and most severe in distal muscle groups. Central chromatolysis of anterior horn cells and loss of dorsal root ganglion cells occurred. In muscle, there was evidence both of recent denervation atrophy, with scattered small angulated fibres, and of more longstanding denervation, with grouped atrophy. The phrenic nerves, diaphragm, and intercostal nerves and muscles were involved. The finding of scattered necrotic muscle fibres suggested a coexisting primary myopathy in some patients.

Several factors were considered possible causes of the polyneuropathy. In the statistical analysis, it was not possible to assemble a satisfactory control group because during the period of the study no patient who had been septic and critically ill had had entirely normal electrophysiological studies. We therefore compared test results in all patients with our control laboratory values and then compared the mild and severe polyneuropathy groups. The results suggested that recognized toxic, nutritional or metabolic factors were not responsible. Aminoglycosides, potentially neurotoxic agents, were not always given to patients before the diagnosis of polyneuropathy. Although mean trough aminoglycoside levels were mildly elevated, only 1 patient developed ototoxicity. The serum levels did not correlate with the severity of polyneuropathy. A local toxic cause is unlikely because a polyneuropathy developed in the critical care units of several hospitals in our area; moreover, a similar polyneuropathy has been reported in one critical care unit in the United States (Roelofs *et al.*, 1983).

Specific nutritional deficiency was unlikely, because all patients were given total parenteral nutrition which included B vitamins, chromium, vitamin E and linolenic acid (Jeejeebhoy *et al.*, 1977; Freund *et al.*, 1979; Harding *et al.*, 1982; Holman *et al.*, 1982; Victor, 1984). Autopsy did not disclose other evidence of nutritional deprivation, such as Wernicke's disease. The levels of serum albumin and blood lymphocyte counts were reduced, suggesting 'nonspecific' nutritional depletion (Fischer, 1976), but the precise nature of this condition is still in doubt. We cannot exclude an as yet unrecognized form of nutritional deficiency.

Generalized weakness and fibrillation potentials on needle electromyography have been attributed to acute hypotensive episodes (Rivner *et al.*, 1983). Examination of the spinal cord in our patients disclosed anterior horn cell changes suggestive of ischaemia in only 2 patients, and this probably occurred preterminally. The electrophysiological and morphological changes observed in sensory nerves cannot be explained by spinal cord ischaemia. Hypophosphataemia has been linked to polyneuropathy (Weintraub, 1976; Yagnik *et al.*, 1982; Straschill and Klatt, 1983) and failed weaning (Agusti *et al.*, 1984; Aubier *et al.*, 1985), but our patients did not have consistently reduced phosphate levels. Elevated glucose levels were secondary to sepsis rather than to diabetes mellitus.

Critical illness polyneuropathy is unlikely to be a previously recognized type of polyneuropathy that happens to complicate critical illness. Axonal degeneration of motor and sensory fibres and normal cerebrospinal fluid distinguish it from the

Guillain-Barré syndrome in most patients (Bolton *et al.*, 1986). Although some of our patients had disorders associated with chronic neuropathy, for example diabetes mellitus, renal failure and carcinoma, they were not known to have neuropathy before admission to the unit, and these disorders are unlikely to have caused an acute, monophasic polyneuropathy. Dialysis was not required in any of our patients. Neuropathy has been reported to complicate chronic obstructive pulmonary disease (Valli *et al.*, 1984), a common disorder in our patients. The patients reported, however, were not critically ill and the polyneuropathy was relatively mild. A further report of polyneuropathy among patients with burns (Henderson *et al.*, 1971) described only abnormalities in conduction velocity and the morphology of the peripheral nerves was not assessed.

The polyneuropathy developed during the course of sepsis and multiple organ failure and improved as the critical illness subsided. The relationship suggests that the pathogenesis of failing systemic organs and peripheral nerve damage may be the same. The precise mechanism remains speculative. Light and electron microscopic study of peripheral nerves revealed features consistent with a primary axonal degeneration of nerve fibres, but no structural changes of a specific nature (Dyck *et al.*, 1984) to identify the mechanism. The observation of central chromatolysis of anterior horn cells further supports the hypothesis that primary axonal damage occurs, possibly affecting axonal transport systems (Ochs, 1984). Failure of these energy-dependent systems due to mitochondrial failure in sepsis (Chaudry *et al.*, 1979) may predominantly involve distal nerve segments (Spencer and Schaumburg, 1984) in advanced sepsis, although comparable changes to those observed in peripheral nerve were not seen in the CNS. Low (1984) described differences between the blood-brain and blood-nerve barrier. Among these are a marked susceptibility of the blood-nerve barrier to increased permeability induced by histamine and serotonin (Olsson, 1966). Several mediators of the septic syndrome are known to have a histamine-like action (Lefer, 1985). Circulating 'toxins' could thereby gain access to the endoneurial space and directly damage the axon.

Further investigations are needed to explore these and other possibilities. There have been no studies in animal models of the impact of sepsis and multiple organ failure on the central or peripheral nervous systems.

Recognition of critical illness polyneuropathy has important practical implications. It is, along with a catabolic myopathy, the most likely cause of 'unexplained' difficulty in weaning from the ventilator as sepsis and multiple organ failure resolve. Conventional signs of polyneuropathy may be absent and only electrophysiological studies will establish the diagnosis. Recovery from the polyneuropathy may occur relatively quickly, but active physiotherapy to avoid pressure sores and contractures and active rehabilitation are important in management. Our studies provide no evidence that current methods of intensive care management, such as the use of antibiotics or total parenteral nutrition, cause the polyneuropathy. In fact, all medical and surgical means to improve sepsis and multiple organ failure will probably lessen the incidence and severity of this complication. Thus methods

to prevent sepsis, such as the use of sterile techniques for invasive procedures, are of prime importance in the prevention of the syndrome and the polyneuropathy.

### *Muscle Wasting*

In 1892, Sir William Osler provided a perceptive description of sepsis. He cited, as an example, a wound infection which was complicated by the systemic signs of severe rigor, temperature rises to 103 or 104 deg, profuse sweating and chills which were repeated at intervals either daily or every other day. Pyrexia might only be slight in the interval. His last sentence states 'The constitutional evidence is marked, and there are loss of appetite, nausea, vomiting, and as the disease progresses rapid loss of flesh.' Recent investigations have indicated that the loss of flesh is due to a catabolic myopathy, but it has been assumed that this is the sole cause of weakness of respiratory muscles during critical illness—a state of respiratory muscle fatigue (Roussos and Macklem, 1982). The basic mechanism is initiated by interleukin-1, stimulated by the macrophage system, which increases prostaglandin E2 production, thereby activating lysosomal proteases in muscle (Baracos *et al.*, 1983; Clowes *et al.*, 1983). Elevated levels of catecholamine and cortisol may also induce muscle breakdown.

The discovery that polyneuropathy and resulting denervation of muscle are frequent complications of critical illness indicates that the causes of muscle wasting and respiratory fatigue in this syndrome are now twofold: denervation atrophy and catabolic myopathy.

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## NONSYSTEMIC VASCULITIC NEUROPATHY

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### SUMMARY

Among 65 patients with necrotizing vasculitis, 45 had systemic and 20 had nonsystemic vasculitic neuropathy. In nonsystemic vasculitic neuropathy, clinically only nerves are affected; there are no, or few, constitutional symptoms or serological abnormalities. The clinical and pathological features are those of an ischaemic neuropathy caused by a necrotizing vasculitis of small arterioles. These 20 patients had neuropathic symptoms for a median time of 11.5 yrs (range 1–35 yrs). The clinical pattern of neuropathy was that of multiple mononeuropathy in 13, asymmetric neuropathy in 4, distal polyneuropathy in 3, and sensory polyneuropathy in 1. As compared with their initial evaluation, 8 are now worse, 5 are better, 4 are approximately the same, and 3 are dead from unrelated causes. Prednisone was thought to prevent the development of new lesions in some cases. By contrast, of the 41 patients with systemic necrotizing vasculitis whose outcome is known, 12 are dead (median time, 1.5 yrs, range 3 months–8 yrs) and 29 are alive (median time, 6 yrs, range 6 months–22 yrs).

### INTRODUCTION

Characteristically, in systemic vasculitic neuropathy (SVN), first one, then another, and then other nerves become affected, each acutely. This pattern is referred to as 'mononeuritis multiplex' or 'multiple mononeuropathy'. SVN may be a component of polyarteritis nodosa, hypersensitivity states, systemic lupus erythematosus, rheumatoid arthritis, Wegener's granulomatosis, or Churg-Strauss syndrome (Kusmaul and Maier, 1866; Wegener, 1936; Kernohan and Woltman, 1938; Churg and Strauss, 1951; Zeek, 1953; Conn and Dyck, 1984). Widespread occlusion of epineurial arterioles causes multifocal ischaemic central fascicular or sector degeneration of nerve fibres (Dyck *et al.*, 1972, 1984). Necrotizing vasculitis does not always cause a multiple mononeuropathy; asymmetric and symmetric polyneuropathies have been described (Wees *et al.*, 1981; Kissel *et al.*, 1985). Because multiple mononeuropathy may also occur in diabetes, leprosy, sarcoidosis, inherited tendency to pressure palsies, neoplastic infiltration, lymphomatous



compression of nerve, and haemorrhagic diathesis, identification of multiple mononeuropathy is not synonymous with the diagnosis of necrotizing vasculitis.

In SVN, several tissues characteristically become involved. Selective involvement of only one tissue has also been described. Possibly these latter cases are tissue-specific forms of necrotizing vasculitis. Isolated angiitis of the skin (Winkelmann and Ditto, 1964; Diaz-Perez and Winkelmann, 1974; Gilliam and Smiley, 1976; Fauci *et al.*, 1978; Fan *et al.*, 1980), brain (Fauci *et al.*, 1978; Cohen and Hurd, 1981; De Reuck *et al.*, 1982; Cupps *et al.*, 1983), of other organs (Liebow, 1973; Israel *et al.*, 1977), and of nerves (Kernohan and Woltman, 1938; Torvik and Berntzen, 1968) has been described. Torvik and Berntzen (1968), reporting on the clinical, biopsy, and necropsy findings in 3 elderly patients, suggested that vasculitis might remain localized to muscles and peripheral nerves. Recently, Kissel *et al.* (1985) noted that many of their 16 patients whose sural nerve biopsies showed necrotizing vasculitis did not have a definable collagen vascular disease and that peripheral neuropathy might be the sole manifestation of vasculitis. They found that a symmetric polyneuropathy occurred in a higher proportion of cases than had been documented previously.

In the last twenty years we have encountered 20 patients with multiple mononeuropathy or other neuropathic patterns attributed to nonsystemic vasculitic neuropathy (NSVN). The features were: (1) only peripheral nerves were affected, even after many years in some cases; (2) joints, visceral organs, and skin remained unaffected; (3) there were no, or only mild, constitutional symptoms or serological abnormalities; (4) the disease was indolent and protracted over years and appeared not to be life-threatening; (5) the severity of nerve symptoms and deficits varied considerably; and (6) an underlying indolent necrotizing vasculitis of small epineurial arterioles appeared to be responsible.

## MATERIAL AND METHODS

### *Case Selection*

The patients included here were selected, after review of their medical records and sural nerve tissue slides, from the following sources: (1) case cards (kept since 1964) of patients with multiple mononeuropathy or asymmetric neuropathies; (2) patients with pathological alterations suggestive or diagnostic of necrotizing vasculitis in their nerve biopsy tissue; and (3) patients whose nerve biopsy was not diagnostic but another tissue was diagnostic of necrotizing vasculitis at biopsy or necropsy.

### *Histologic Methods*

Transverse and longitudinal paraffin sections of sural nerve were stained with haematoxylin and eosin, trichrome, luxol-fast blue and periodic acid-Schiff, methyl violet, Congo red, and Weigert's elastic stain. Transverse semithin (0.75  $\mu$ m) epoxy sections of nerves fixed with aldehyde and osmium tetroxide were stained with phenylenediamine and methylene blue. One hundred or more teased fibres were prepared from each nerve after initial separation of the nerve into 50 strands.

*Criteria for Pathological Diagnosis of Necrotizing Vasculitis*

For the pathological diagnosis of necrotizing vasculitis, two criteria had to be fulfilled: (1) inflammation of the vessel wall (infiltration by mononuclear or polymorphonuclear cells); and (2) necrosis of the wall (especially of the tunica media). Pathological alterations considered to be suggestive but not diagnostic of necrotizing vasculitis were: (1) mural or perivascular inflammation without tissue necrosis, with or without intimal proliferation; or (2) evidence of necrosis or previous necrosis of the arteriole wall without inflammation, with or without intimal proliferation and with or without focal or multifocal fibre degeneration.

## RESULTS

*Systemic Vasculitic Neuropathy*

Of the 45 patients, 32 had polyarteritis nodosa or hypersensitivity vasculitis, 4 had the Churg-Strauss syndrome, 3 had Sjögren's syndrome, 2 had rheumatoid arthritis, and 1 each had Wegener's granulomatosis, scleroderma, systemic lupus erythematosus, and acquired immune deficiency disease. Separation of syndromes was based on conventional clinical and serological features and followed published criteria.

Only patients with a tissue diagnosis of necrotizing vasculitis were included. The sural nerve biopsy was diagnostic in 26, suggestive in 13, and nondiagnostic in 6 patients. In the last two groups, the pathological diagnosis had been based on biopsied muscle, kidney or liver, or postmortem tissue. Sural nerve biopsy was diagnostic in 26 of 45 (58%) whereas gastrocnemius muscle biopsy was diagnostic in 3 of 12 (25%). Meaningful comparisons of the diagnostic yield of nerve and other tissues was not possible because other tissues were obtained in too few cases.

The pathological alterations of vessels and the spatial distribution and type of fibre degeneration were like those described in a previous report (Dyck *et al.*, 1972). Vasculitic changes were found in epineurial arterioles 75 to 250  $\mu$ m in diameter (figs 1, 2). Arterioles in endoneurium showing vasculitis were not expected or found, because the endoneurium seldom contains arterioles. In systemic necrotizing vasculitis, focal or multifocal fibre loss was typical (fig. 3). In most cases, central fascicular or sector (the base abutting the perineurium) loss of fibres was observed. In severe neuropathy, fibre loss was usually generalized. In teased fibre preparations, the typical abnormality was axonal degeneration. Segmental demyelination and remyelination was encountered in some teased fibres in all nerves. This was judged (without quantitation) to be slightly higher in the nerves of patients than in nerves of healthy subjects.

Of the 45 patients (25 women and 20 men), we were able to ascertain the present medical status of 41 (12 dead and 29 alive). Death occurred at a median time of 1.5 yrs (range 3 months–8 yrs) after onset of symptoms and was usually attributable to vasculitis. For the living patients, the median time from onset of symptoms to the time of final evaluation was 6 yrs (range 6 months–22 yrs). The general and neuropathic status of approximately two-thirds of the living patients were better than at their first evaluation. Approximately one-third were worse. All living

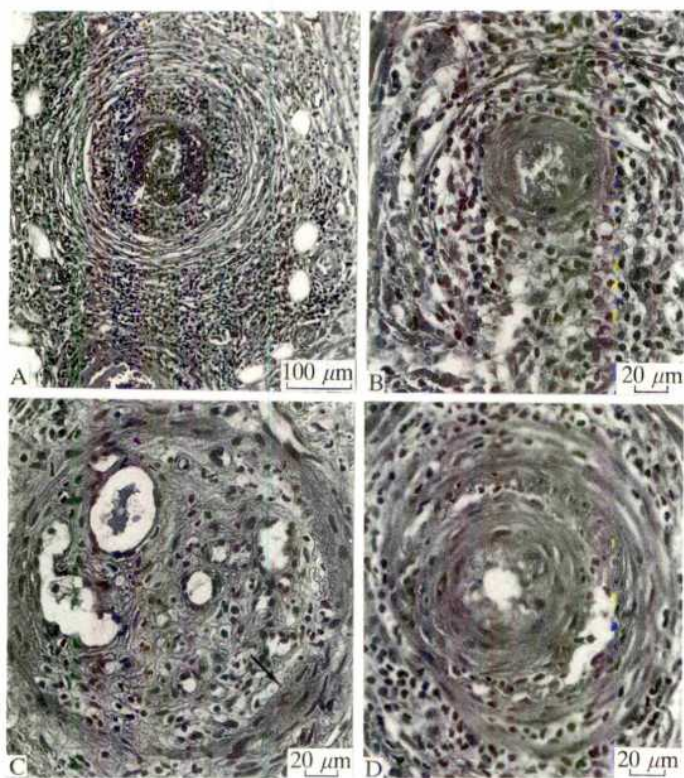


FIG. 1. Transverse paraffin sections of sural nerve, showing epineurial arterioles from patients with SVN (haematoxylin and eosin). A, the architecture is severely altered from normal; prominent features are virtual obliteration of the lumen, fibrinoid necrosis (white arrow), polymorphonuclear and mononuclear cell infiltration of the vessel wall, and disappearance (necrosis) of the tunica media. B, intimal proliferation, virtual disappearance of lumen, necrosis of media, and mononuclear cell infiltration. C, the crescent of tunica media (arrow) remaining extends from about 10 to 6 o'clock; the proliferated intima is recanalized; a few perivascular mononuclear cells surround the vessel. D, disorganization of intima and media with infiltration by mononuclear cells.

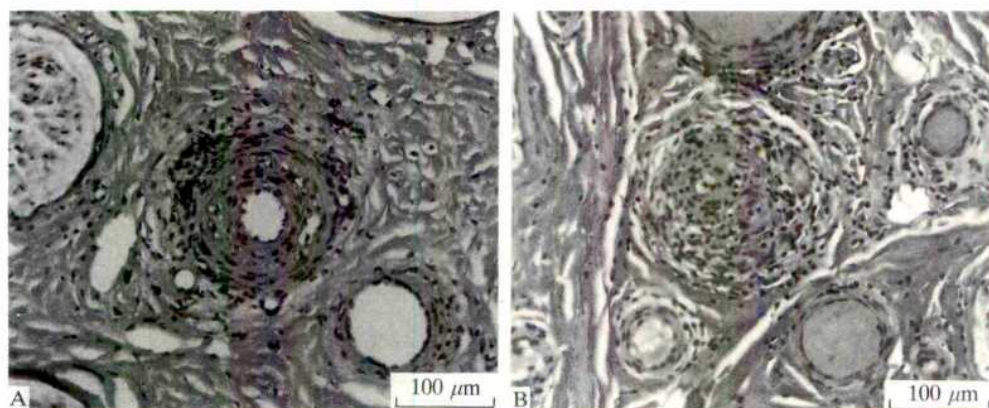


FIG. 2. Transverse paraffin sections of sural nerve, showing epineurial arterioles from patients with SVN (haematoxylin and eosin). The changes affect arterioles smaller than those illustrated in fig. 1. A, intimal proliferation, narrowing of lumen, disorganization of media, and inflammatory cell infiltration; haemosiderin was found adjacent to this vessel (not shown), indicative of previous bleeding. B, complete obliteration of lumen, inflammatory cell infiltration, and necrosis of the media.



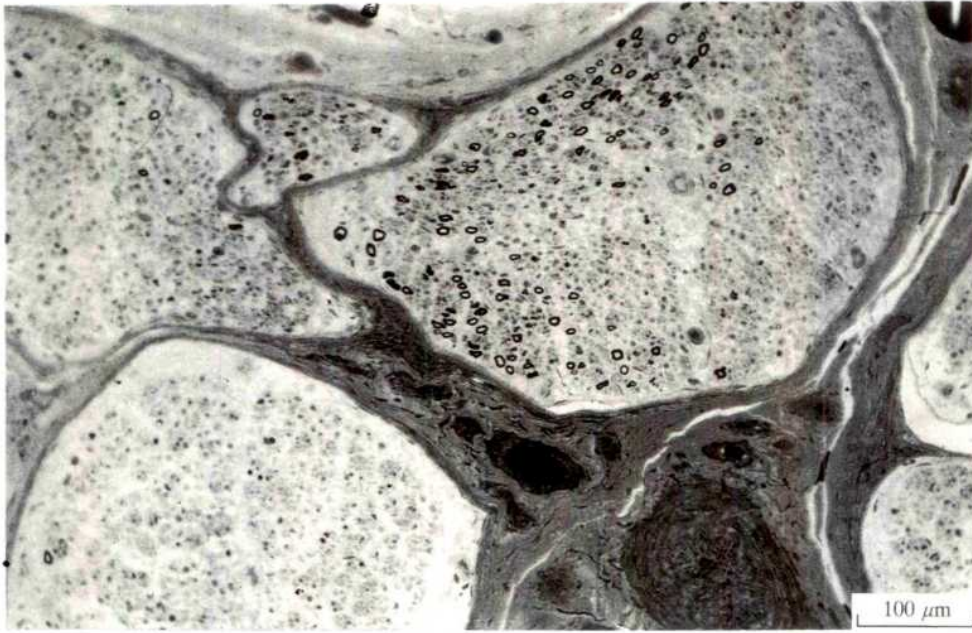


FIG. 3. Semithin transverse epoxy section of sural nerve from a patient with SVN, showing the prominent multifocal fibre loss. Only a crescent of one fascicle contains myelinated fibres (glutaraldehyde and osmium tetroxide fixation).

patients, except for a few who recovered, are receiving prednisone or other drug therapy.

#### *Nonsystemic Vasculitic Neuropathy*

Included in this group were 5 cases with diagnostic pathological features of necrotizing vasculitis in sural nerve tissue and 15 cases in which the features were suggestive but not diagnostic. Inclusion of the latter group of patients appeared to be justified because the pathological changes were in keeping with the diagnosis of necrotizing vasculitis and the clinical features were the same in the suggestive and diagnostic groups. Furthermore, in many of the nerves with nondiagnostic features of necrotizing vasculitis, multifocal fibre loss suggested ischaemic damage. Only cases with a duration of symptoms longer than 1 yr were included.

The disease process appeared to affect smaller epineurial arterioles in NSVN than in SVN and the process tended not to be as severe (figs 4, 5). None of the 20 patients had diabetes mellitus as evaluated by fasting plasma glucose and glycosylated haemoglobin concentrations. Sarcoidosis was excluded by clinical features, normal angiotensin-converting enzyme value and lack of histological features for that diagnosis.

Determining that the patients did not have focal inflammatory-demyelinating lesions was more problematic. Two patients had electrophysiological features of mild focal block. We decided that these patients did not have inflammatory-

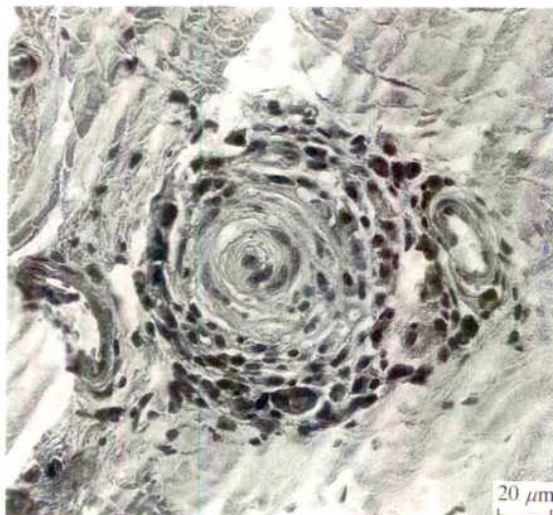


FIG. 4. Transverse paraffin section of sural nerve from a patient with NSVN, showing involvement of a small epineurial arteriole with occlusion of the lumen, disorganization and necrosis of the media, and mural and perivascular mononuclear cell infiltration (haematoxylin and eosin).

demyelinating lesions because the clinical course was compatible with multiple mononeuropathy due to ischaemia, inflammation was confined to epineurial arterioles and there were other features indicative of necrotizing vasculitis. Also, focal or diffuse endoneurial mononuclear infiltrates of the type encountered in inflammatory-demyelination were not encountered, fibre loss was focal or multifocal, and axonal degeneration predominated over segmental demyelination and remyelination.

The mean age at onset of symptoms for these 20 patients (13 women and 7 men) was 51.1 yrs (median 53.5 yrs, range 23–74 yrs). At the time of the last follow-up examination or death, they had had neuropathic symptoms for a mean of 11.2 yrs (median 11.5 yrs, range 1–35 yrs).

The pattern of neuropathic involvement was multiple mononeuropathy in 12 patients, asymmetric neuropathy in 4, symmetric distal sensorimotor polyneuropathy in 3, and sensory polyneuropathy in 1 (Table 1). In those with multiple mononeuropathy, the symptoms and deficits followed the temporal and spatial patterns suggestive of ischaemic injury of peripheral nerves. In an affected nerve, the symptoms were generally subacute in onset, reached a peak in hours or days, remained static for a time, and might then resolve. From the symptoms and findings we inferred that all populations of nerve fibres (motor and sensory and all sizes) were affected. The symptoms reflected both hyperactivity and hypoactivity, as is characteristic of neuropathies with axonal degeneration (Dyck *et al.*, 1976; Thomas, 1974, 1984), especially acquired neuropathies (Dyck *et al.*, 1981). The symptoms included muscle weakness and atrophy, paraesthesiae and pain (burning, aching, lancinating and other), and sensory deficits. When major limb nerves became



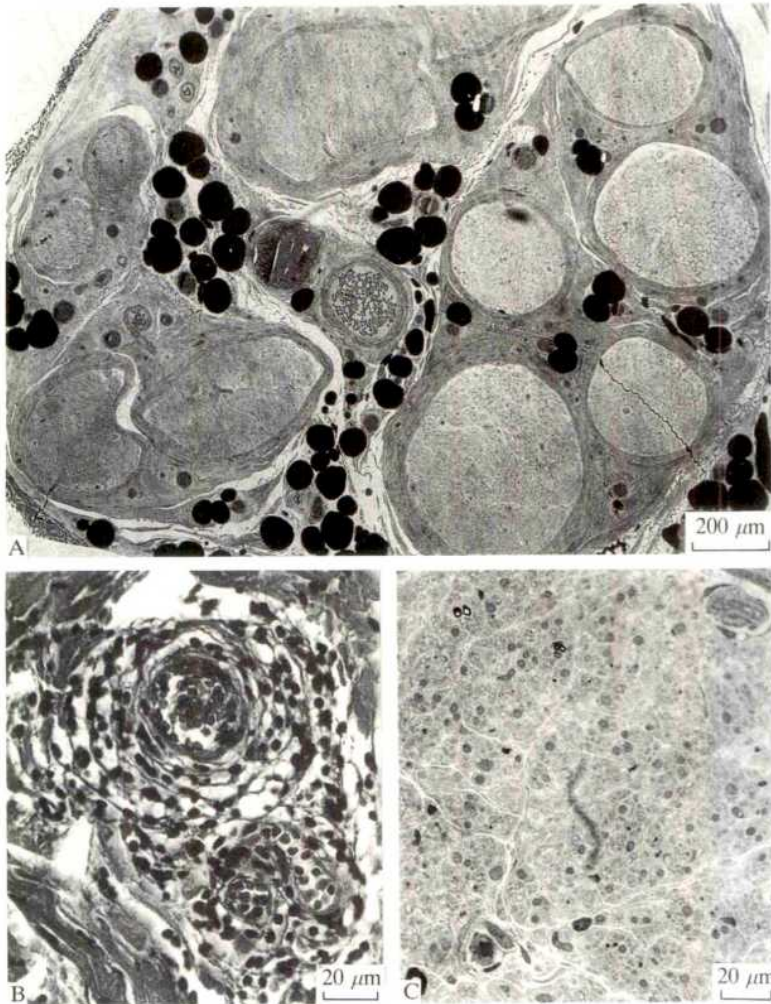


FIG. 5. Transverse sections of sural nerve of a patient with nonsystemic vasculitic symmetric sensory polyneuropathy. A, C, semithin epoxy section of nerve, showing severe loss of myelinated fibres (glutaraldehyde and osmium tetroxide fixation). B, mononuclear cell infiltration of mural and perivascular region and medial necrosis; the lumen is not occluded.

affected, the neuropathic deficit might persist for many years. Excessive sensitivity and pain, although lessening over months or years, were the most disabling symptoms.

Twelve patients had progression of their disease in a pattern of multiple mononeuropathy. The number of events (acute or subacute onset of new neurological symptoms or deficits in the distribution of a peripheral nerve) suffered by these patients averaged 6.3 (median 5.5, range 3–11). Approximately two-thirds had their first event in the lower limbs, the majority within the distribution of the sciatic nerve. Otherwise, the nerves affected formed no clear pattern of distribution or order of involvement. Events affected the lower extremity 50% of the time, upper

TABLE 1. CLINICAL FEATURES OF PATIENTS WITH NONSYSTEMIC VASCULITIC NEUROPATHY

| Case | Age/sex | Duration of symptoms (yrs) | NDS | Pattern of neuropathy | Alive (A) or dead (D) | Sural nerve diag. | ESR (mm/h) |
|------|---------|----------------------------|-----|-----------------------|-----------------------|-------------------|------------|
| 1    | F/50    | 18                         | 71  | MM                    | A                     | ±                 | 27         |
| 2    | M/78    | 10                         | 51  | MM                    | D                     | ±                 | 32         |
| 3    | M/46    | 15                         | 0   | DP                    | A                     | ±                 | 2          |
| 4    | F/57    | 13                         | 10  | MM                    | A                     | ±                 | —          |
| 5    | F/69    | 4                          | 19  | MM                    | A                     | ±                 | 5          |
| 6    | F/59    | 35                         | 34  | MM                    | A                     | ±                 | 21         |
| 7    | M/63    | 1                          | 15  | MM                    | A                     | ±                 | 8          |
| 8    | F/72    | 19                         | 40  | MM                    | A                     | +                 | 55         |
| 9    | F/87    | 13                         | 88  | AN                    | A                     | ±                 | 8          |
| 10   | F/60    | 2                          | —   | DP                    | D                     | ±                 | 43         |
| 11   | F/70    | 6                          | 81  | MM                    | A                     | ±                 | 9          |
| 12   | F/45    | 6                          | 21  | MM                    | A                     | ±                 | 40         |
| 13   | F/71    | 2                          | 12  | AN                    | A                     | ±                 | 62         |
| 14   | F/69    | 6                          | 19  | DSP                   | A                     | +                 | 50         |
| 15   | M/34    | 11                         | 5   | MM                    | A                     | ±                 | 2          |
| 16   | F/60    | 9                          | 81  | DSP                   | A                     | +                 | 8          |
| 17   | M/55    | 16                         | 40  | MM                    | A                     | ±                 | 16         |
| 18   | F/58    | 13                         | 19  | MM                    | ?                     | ±                 | 2          |
| 19   | M/69    | 15                         | 73  | AN                    | ?                     | +                 | 22         |
| 20   | M/76    | 12                         | 59  | AN                    | D                     | ±                 | 22         |

NDS = Neurological Disability Score. This is a summated score of test items in the neurological examination. Weakness is graded: 0 = no weakness, 1 = 25%, 2 = 50%, 3 = 75% or 4 = 100%. Reflexes are graded: 0 = normal, 1 = diminished or 2 = absent. Sensation is graded as for reflexes.

Pattern of neuropathy: MM = multiple mononeuropathy, DP = symmetric distal polyneuropathy, AN = asymmetric polyneuropathy, DSP = symmetric distal sensory polyneuropathy.

Sural nerve diagnosis: + = diagnostic, ± suggestive, but not diagnostic.

extremity 41%, thoracic roots or dermatomes 7%, and cranial nerves 2%. The numbers of patients having events affecting specific nerves are shown in Table 2. Although the nerves commonly affected were the ulnar, peroneal, and median, the majority of events did not affect sites of nerves commonly subject to compression or entrapment. The nerve conduction and electromyographic features were typical of a multifocal process of nerves with axonal degeneration. In 2 cases, features compatible with focal conduction block were encountered.

Second in frequency was a pattern of a symmetric or asymmetric polyneuropathy affecting distal aspects of limbs. One patient had a predominantly sensory neuropathy with severe sensory ataxia.

Haematological indices and urinalysis results generally were normal. Leucocytosis was not found. The ESR averaged 22.8 mm/1 h (Westergren; range 2–62 mm/1 h) and was abnormal in 7 patients ( $\geq 50$  mm in 1 h in 2 and  $\geq 40$  mm in

TABLE 2. NERVE INVOLVEMENT IN 12 PATIENTS WITH MULTIPLE NONSYSTEMIC VASCULITIC MONONEUROPATHIES

| <i>Nerve</i>                                                        | <i>No. of patients</i> |
|---------------------------------------------------------------------|------------------------|
| Ulnar                                                               | 9                      |
| Peroneal                                                            | 7                      |
| Median                                                              | 6                      |
| Sciatic, tibial, lower extremity sensory nerves                     | 5*                     |
| Radial, upper extremity sensory nerves                              | 4+                     |
| Femoral, thoracic roots or cutaneous nerves, distal lower extremity | 3±                     |
| Distal upper extremity                                              | 2±                     |
| Trigeminal, axillary, obturator, lumbar plexus, vagus               | 1                      |

\* Lateral cutaneous nerve of the thigh in 1, sural in 1, medial plantar in 1, other in 2. + More than one nerve. ± Digital nerve in 2, other in 2.

1 h in 5). The cellular content of the CSF was not increased, and the protein content averaged 0.56 g/l (range 0.16–1.01 g/l  $\geq 0.50$  g/l in 8 of 17 patients). Serum antinuclear antibody was measured in 11 cases; it was absent in 7, reactive undiluted in 2, and reactive diluted at 1:80 in 1. Rheumatoid factor was measured in 6 cases and was negative in 4 and reactive undiluted in 1. Cryoglobulin was absent in the 7 cases tested. Serum and a 24 h urine specimen were tested for monoclonal proteins in 12 cases; none was found.

Three of the patients are dead, 1 from a presumably unrelated heart attack, 1 from massive pulmonary embolism during hospital admission for ischaemic heart disease, and 1 from cardiorespiratory arrest (according to the death certificate). It was unclear whether any had died from complications of their disease. Of the remaining 17 patients, 12 walk without assistance, 4 require a walking frame, and 1 is confined to a wheelchair. Their present neuropathic condition is thought to be worse in 8, better in 5, and approximately the same in 4, compared with their initial evaluation.

Treatment had not been sufficiently systematic or controlled to permit critical evaluation of efficacy. In several patients, development of new nerve lesions ceased when prednisone therapy was begun. In these cases, symptoms in already damaged nerves did not resolve more rapidly than in patients without treatment.

## DISCUSSION

Do patients with NSVN have a tissue-specific vasculitic disorder affecting nerve? Or do they simply represent early, mild or unusual manifestations of systemic necrotizing vasculitis? Judging by severity of nerve involvement and comparison with systemic disease, selective involvement of nerve is not explained by lack of severity. Also, we concluded that sufficient time had elapsed for systemic symptoms to be manifested. In earlier reports the duration of illness had been much shorter than in our patients. Kernohan and Woltman's (1938) patient lived only a few



months. Torvik and Berntzen's (1968) patients were followed for 1, 3, and 4 yrs. In the 16 patient series of Kissel *et al.* (1985), the 4 patients without systemic features had durations of 4, 6, 8, and 24 months. On average, our patients had symptoms for more than a decade, and 1 patient had them for 35 yrs.

The prognosis in NSVN is different from that in SVN, another reason for separation of the disorders. In our series, death attributed to disease occurred in almost one-third of the patients with SVN. By contrast, none of the patients with NSVN died from their disease. This difference is not due to duration of follow-up because patients with NSVN were followed for longer times than were those with SVN. Another possible reason for separating the disorders is that in NSVN the process appeared to affect smaller arterioles and to be more indolent. The difference in natural history has implications for therapy. Less therapy-related side effects and risks are justified in NSVN than SVN.

Like other authors (Wees *et al.*, 1981; Kissel *et al.*, 1985), we found clinical patterns of nerve involvement other than multiple mononeuropathy. An unexpected pattern was that of a relatively pure symmetric sensory polyneuropathy.

Is NSVN the same disorder as multifocal demyelinating neuropathy with persistent conduction block (Lewis *et al.*, 1982)? (Two of our patients had conduction block.) Lewis *et al.* considered the possibility of vasculitis but decided against it for the following reasons: (1) long history of progression without systemic disorder; (2) consistently negative laboratory results (presumably no serological abnormalities and normal ESR); (3) demyelinating features in the electromyographic examination and on nerve biopsy; and (4) failure to find necrotizing vasculitis on nerve biopsy.

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# ENCEPHALOPATHY AND MYELINOLYSIS AFTER RAPID CORRECTION OF HYPONATRAEMIA<sup>1</sup>

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## SUMMARY

Considerable controversy has followed the recent publication of studies indicating that central pontine myelinolysis is caused by rapid correction of hyponatraemia. Alternative suggestions have been that myelinolysis is due to uncorrected hyponatraemia, that it occurs only with over-correction of hyponatraemia or that it is due to coincidental hypoxia. The following experiments were undertaken to clarify the relationship between myelinolysis and derangements of serum sodium and their treatment. Severe hyponatraemia ( $[\text{Na}^+] \leq 122 \text{ mmol/l}$ ) was produced in three groups of rabbits by injection of vasopressin and 5% dextrose in water. Rabbits with severe uncorrected hyponatraemia sustained for seven days or more did not show myelinolysis at autopsy. Myelinolytic lesions did develop in 3 of 7 rabbits in a second group in which corrective infusion of hypertonic saline was administered after only three days of severe hyponatraemia. Neurological deterioration also occurred in rabbits in the third group which received hypertonic saline within 24 h of developing severe hyponatraemia. In this group no lesions were apparent at autopsy. No animal became hypernatraemic with correction. These results indicate that even prolonged severe hyponatraemia does not lead to myelinolysis if it remains uncorrected, but that rapid correction of hyponatraemia, without over-correction, can cause neurological disease. Accordingly, a rapid rise in serum sodium should be avoided.

## INTRODUCTION

Controversy has permeated the recent medical and neurological literature on the management of hyponatraemia. The primary issue is whether treatment of hyponatraemia causes central pontine and extrapontine myelinolysis. All authors agree that hyponatraemia can cause morbidity and mortality, but some do not recognize the neurological dangers of rapid correction. The results of animal experiments have been stated to be 'conflicting' and the relationship of myelinolysis

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to correction of hyponatraemia questioned (Narins, 1986). That author and others have advised vigorous treatment of hyponatraemia with hypertonic saline (Arieff *et al.*, 1976, Arieff and Schmidt, 1980; Ayus *et al.*, 1982, 1983; Fraser and Arieff, 1984). Other investigators have related myelinolysis to the rapid correction of hyponatraemia and therefore advised moderation in correcting the sodium (Laureno, 1980, 1981, 1983, 1985; Kleinschmidt-DeMasters and Norenberg, 1981*a, b*; Sterns *et al.*, 1986). Since hyponatraemia is a common medical disorder which occurs in association with a variety of illnesses, resolution of these controversies is essential. The present study was undertaken to clarify these issues.

The term central pontine myelinolysis (CPM) was selected by Adams *et al.* (1959) to denote the symmetric area of myelin damage found in the centre of the basis pontis. Large CPM lesions produce quadriplegia and pseudobulbar palsy, and occasionally neuro-ophthalmic features (Mani and Laureno, 1986). Small lesions are often asymptomatic. This disease has now been recognized throughout the world, in both sexes and in all age groups. In approximately 10% of reported cases symmetric extrapontine lesions have been found in the thalamus, internal capsule, cerebellum, or lower levels of cerebral cortex and subadjacent white matter (Wright *et al.*, 1979). Although the majority of patients with CPM are alcoholic, the disease has been described in a variety of other medical settings (Berry and Olszewski, 1963; Goebel and Herman-Ben Zur, 1976; Burcar *et al.*, 1977). Regardless of the underlying medical illness, derangements of serum sodium, especially hyponatraemia, have been identified in many patients and appear to be the factor most closely associated with CPM (Adams, 1962; Aleu and Terry, 1963; Berry and Olszewski, 1963; Conger *et al.*, 1969; Paguirigan and Lefken, 1969; Goebel and Herman-Ben Zur, 1976; Tomlinson *et al.*, 1976; Burcar *et al.*, 1977; Wright *et al.*, 1979; Norenberg *et al.*, 1982). Tomlinson *et al.* (1976) raised the possibility that therapy with hypertonic saline was the crucial factor in the pathogenesis of CPM. Other investigators also documented a history of correction of hyponatraemia in patients with pontine and extrapontine lesions at autopsy (Wright *et al.*, 1979; Norenberg *et al.*, 1982).

As a result of these observations in man, animal studies were undertaken. Laureno (1980, 1981, 1983) was able to produce pontine and extrapontine lesions in dogs by rapid correction of hyponatraemia. The similar experiments of Kleinschmidt-DeMasters and Norenberg (1981*a, b*) in rats resulted in extrapontine lesions, a finding which has recently been confirmed in another laboratory (Ayus *et al.*, 1985*c*).

Despite the mounting clinical and experimental evidence of an association between the correction of hyponatraemia and CPM, the controversy delineated above persists. It has been suggested that hyponatraemia itself, not its rapid correction, may lead to myelinolysis (Arieff, 1981) or that myelinolysis occurs only when hyponatraemia is over-corrected (Fraser and Arieff, 1984; Ayus *et al.*, 1985*a, b*), or that myelinolysis is due to hypoxaemia during hyponatraemic seizures with respiratory arrest (Arieff, 1986). The experiments described below were

designed to investigate the following issues in another species. (1) Can severe protracted uncorrected hyponatraemia alone cause myelinolysis? (In previous studies uncorrected animals had severe hyponatraemia for only three or four days.) (2) Can the rapid correction of hyponatraemia cause CPM in rabbits? (3) Does the duration of hyponatraemia before correction affect the risk of developing CPM?

## METHODS

Experimental hyponatraemia was induced by a method adapted from previous studies (Arieff *et al.*, 1976; Kleinschmidt-DeMasters and Norenberg, 1981a; Laureno, 1983). Fifty-five New Zealand white rabbits weighing 3 to 5 kg were injected with intramuscular vasopressin tannate (Pitressin, 5 U/ml) and intraperitoneal 5% dextrose in water (D5W). Before each treatment the animals were sedated with 2.5 ml ketamine hydrochloride (Ketalar) i.m. and 0.5 ml xylazine (Rompun) i.m. The initial dosages were 1 U/kg for vasopressin and 5% of body weight for D5W per day. Later doses were individualized, based on the clinical condition and serum sodium level of each animal in order to maintain severe but nonlethal hyponatraemia. The daily dose ranges were 1 to 3 U/kg for vasopressin and 5 to 13% body weight for D5W; 4 mmol KCl were added to each litre of D5W and additional KCl was provided to those animals whose serum  $[K^+]$  fell below normal on the standard regimen.

The normal serum  $[Na^+]$  in New Zealand white rabbits ranges from 131 to 153 mmol/l with an average of 140 mmol/l (Kaplan and Timmons, 1979; Kozma *et al.*, 1974). The serum  $[Na^+]$  in our rabbits before experimentation was  $145 \pm 7$  mmol/l. The results were expressed as mean  $\pm$  SEM. Since it has been reported that most patients are symptomatic at a serum sodium concentration of 125 mmol/l (Arieff *et al.*, 1976; Arieff and Schmidt, 1980; Fraser and Arieff, 1984) a degree of hyponatraemia below that level (122 mmol/l) was selected as the definition of severe hyponatraemia. Serum  $[Na^+]$  was measured daily throughout the hyponatraemic period.

Rabbits were divided into three experimental groups.

Group I: *Prolonged hyponatraemia: uncorrected* (25 animals). This group received vasopressin and D5W daily in an attempt to maintain severe hyponatraemia for at least 7 days.

Group II: *Sustained hyponatraemia: corrected* (10 animals). When severe hyponatraemia had been sustained for 3 days these animals were treated with 3% saline intraperitoneally. The amount of hypertonic solution used was calculated in each animal to correct the serum sodium concentration up to 130 mmol/l with a single intraperitoneal administration. The sodium deficit (mmol) was calculated by multiplying estimated litres of body water ( $0.5 \times$  kg of body weight) times the difference between the target serum sodium concentration (mmol/l) and the measured serum sodium concentration (mmol/l), i.e.  $Na^+$  deficit =  $0.5 \times$  body weight  $\times$  (target  $[Na^+]$  – measured  $[Na^+]$ ).

Group III: *Brief hyponatraemia: corrected* (20 animals). This group received vasopressin and D5W only until the serum sodium concentration reached 122 mmol/l or less. As soon as severe hyponatraemia was documented, the rabbits were corrected with 3% saline in the same manner as Group II animals.

In all three groups, autopsies were performed at death. Groups II and III animals which survived correction by 21 days or more were killed with intracardiac  $MgSO_4$  or intraperitoneal pentobarbital (Nembutal). Brains were fixed in 10% formalin, sectioned and examined grossly. Specimens of cerebral cortex, basal ganglia, thalamus, midbrain, pons, medulla and cerebellum were studied microscopically with haematoxylin and eosin and luxol-fast blue stains.

TABLE 1. RABBITS WITH PROLONGED<sup>1</sup> SEVERE<sup>2</sup> HYPONATRAEMIA: UNCORRECTED (GROUP I)

| <i>Rabbit no.</i> | <i>Average [Na<sup>+</sup>]<sup>3</sup></i> | <i>Survival (days)<sup>4</sup></i> | <i>Clinical signs</i> | <i>Myelinolysis</i> |
|-------------------|---------------------------------------------|------------------------------------|-----------------------|---------------------|
| 1                 | 115                                         | 10                                 | Equivocally weak      | Absent              |
| 4                 | 103                                         | 10                                 | Very weak rear legs   | Absent              |
| 5                 | 103                                         | 7                                  | Equivocally weak      | Absent              |
| 8                 | 101                                         | 8                                  | Weak rear legs        | Absent              |
| 11                | 116                                         | 9                                  | Equivocally weak      | Absent              |
| 17                | 109                                         | 10                                 | Very weak rear legs   | Absent              |
| 21                | 103                                         | 8                                  | Well                  | Absent              |
| 25                | 113                                         | 7                                  | Diffusely weak        | Absent              |

<sup>1</sup> Severe hyponatraemia maintained for  $\geq 7$  days (measured daily). <sup>2</sup>  $[\text{Na}^+] \leq 122$  mmol/l. <sup>3</sup> Average serum  $[\text{Na}^+]$  during severely hyponatraemic period. <sup>4</sup> Duration of survival with  $[\text{Na}^+] \leq 122$  mmol/l.

## RESULTS

### Group I

Twenty-five rabbits were treated with daily vasopressin and D5W in order to produce prolonged severe hyponatraemia. Nine animals died during the attempt to induce severe hyponatraemia. These animals survived 2 to 7 days of experimentation and had a mean serum  $[\text{Na}^+]$  of 131 mmol/l on the day before being found dead. Another 8 animals were documented to have attained severe hyponatraemia ( $[\text{Na}^+] \leq 122$  mmol/l) but died after less than 7 days of hyponatraemia at this level. These animals lived an average of 4 days with severe hyponatraemia and had a mean serum  $[\text{Na}^+]$  of 104 mmol/l during the hyponatraemic period.

The remaining 8 rabbits (32%) survived at least 7 days with a serum  $[\text{Na}^+] \leq 122$  mmol/l. Survival ranged from 7 to 10 days with an average of 9 days. The serum sodium concentration during the period of severe hyponatraemia ranged from 90 to 122 mmol/l. Clinically, 1 animal appeared well throughout the experiment (mean  $[\text{Na}^+]$  103 mmol/l during the severely hyponatraemic period), 3 were slightly or equivocally weak (mean serum  $[\text{Na}^+]$  115, 103, and 116 mmol/l), and 4 showed definite weakness and lethargy (mean serum  $[\text{Na}^+]$  103, 101, 109, 113 mmol/l (Table 1)). None of the animals had observed seizures; 2 had increased muscle tone. Autopsies of these rabbits revealed no myelinolytic lesions.

### Group II

In 10 animals an attempt was made to maintain the serum  $[\text{Na}^+]$  at or below 122 mmol/l for at least 3 days before rapid correction of hyponatraemia with hypertonic saline. Two animals died before correction. The serum  $[\text{Na}^+]$  of a third could not be raised despite two attempts at correction.

For all of the remaining 7 rabbits, the mean serum  $[\text{Na}^+]$  was  $107 \pm 4$  mmol/l during the severely hyponatraemic period before correction. On treatment with

TABLE 2. RABBITS WITH SUSTAINED<sup>1</sup> SEVERE<sup>2</sup> HYPONATRAEMIA: RAPIDLY CORRECTED (GROUP II)

| <i>Before correction</i> |                                            |                  | <i>After correction</i>                    |                                                 |                                    |                     |
|--------------------------|--------------------------------------------|------------------|--------------------------------------------|-------------------------------------------------|------------------------------------|---------------------|
| <i>Rabbit no.</i>        | <i>[Na<sup>+</sup>] mmol/l<sup>3</sup></i> | <i>Signs</i>     | <i>[Na<sup>+</sup>] mmol/l<sup>4</sup></i> | <i>Signs<sup>5</sup></i>                        | <i>Survival (days)<sup>6</sup></i> | <i>Myelinolysis</i> |
| 26                       | 104                                        | Well             | 130/137                                    | Monoparesis<br>R rear leg (3)                   | 22                                 | Absent              |
| 28                       | 98                                         | Well             | 100/133                                    | Quadriplegia (1)                                | 2 $\frac{1}{2}$                    | Absent              |
| 31                       | 94                                         | Well             | 132/142                                    | Tremulousness,<br>quadriplegia,<br>seizures (1) | 6                                  | Thalamus            |
| 32                       | 114                                        | Well             | 138/144                                    | Diffusely weak,<br>cachectic (17)               | 18                                 | Thalamus            |
| 33                       | 106                                        | Well             | 132/143                                    | Flaccid<br>Monoparesis<br>R rear leg (4)        | 21                                 | Pons,<br>thalamus   |
| 34                       | 107                                        | Well             | 126/135                                    | 'Shaky', startles,<br>equivocally weak (2)      | 21                                 | Absent              |
| 35                       | 92                                         | Slightly<br>weak | 128/129                                    | Quadriplegia (2)                                | 4                                  | Absent              |

<sup>1</sup> Severe hyponatraemia maintained for 3 days. <sup>2</sup> [Na<sup>+</sup>]  $\leq$  122 mmol/l. <sup>3</sup> [Na<sup>+</sup>] immediately before correction. <sup>4</sup> [Na<sup>+</sup>] attained 24 h after treatment with hypertonic saline/[Na<sup>+</sup>] attained 48 h after treatment with hypertonic saline. <sup>5</sup> Number in parenthesis indicates the day after correction on which the neurological signs were first observed. <sup>6</sup> Number of days rabbit survived after correction of hyponatraemia. Animals were killed at 21 days.

hypertonic saline the serum [Na<sup>+</sup>] rose to  $127 \pm 12$  mmol/l (range 100–138 mmol/l) at 24 h postcorrection; this constitutes a mean change in serum sodium concentration of  $24 \pm 11$  mmol/l in 24 h. While hyponatraemic, 6 of 7 rabbits appeared well; 1 was slightly weak. Mortality after correction, however, approached 50% by 1 week with 3 out of 7 rabbits dying within 6 days. Of the remaining 4 animals, 3 lived until they were killed at 21 days after correction; 1 died at 18 days (Table 2). The neurological condition of all 7 rabbits surviving correction worsened following the rapid improvement of hyponatraemia. Severe weakness was the most common problem, affecting 6 out of 7 animals. In 4 cases there was quadriplegia, in 2 monoparesis. Seizures occurred in 1 of the quadriplegic animals. These signs appeared by 4 days after correction in 5 rabbits and by 17 days in 1 animal. The 1 animal without severe weakness was tremulous for several days after correction. On pathological examination there were no gross changes in any of the brains. Three of the 6 animals with severe weakness showed myelinolytic lesions on microscopic section. Rabbit 33 showed a symmetric lesion in the centre of the pons and bilaterally symmetric lesions of the thalamic region involving the nucleus



basalis thalami, nucleus posterior thalami, medial lemniscus and lamina medullaris ventralis (fig. 1). The medial areas of the thalamus were intact, as were the lateral geniculate bodies. Rabbits 31 and 32 had similar bilateral lesions in the thalamus only. The sections demonstrated loss of myelin and oligodendroglia throughout the lesions. Necrosis of all tissue components was evident in the centre of the lesions, whereas in the periphery there were demyelinated areas which contained normal neurons. The lesions were full of macrophages (fig. 2).

### Group III

For these 20 rabbits the intent was to lower serum  $[Na^+]$  in the same manner used for Groups I and II but to correct the sodium derangement within 24 h of attaining severe hyponatraemia. This objective was not attained in 8 animals, some of which died during the induction of hyponatraemia and others which failed to show substantial correction of hyponatraemia despite receiving hypertonic saline.

In the remaining 12 rabbits the serum  $[Na^+]$  before correction was  $106 \pm 13$  mmol/l (range 70–116) and rose to  $131 \pm 7$  mmol/l (range 122–143) by 24 h after treatment with hypertonic saline (Table 3); this increase represents a change in serum  $[Na^+]$  of  $25 \pm 15$  mmol/l (range 8–66). While hyponatraemic, these 12 rabbits showed little morbidity: 2 were slightly weak and 1 had seizures. In contrast, 4 rabbits developed clinical signs 1 to 2 days following correction of hyponatraemia. The neurological abnormalities included spastic diplegia, flaccid quadriparesis, lethargy and flaccid monoparesis. The animals which developed these neurological signs did not differ from animals without neurological deterioration in either the degree of hyponatraemia or the extent of correction at 24 h. However, when serum sodium was measured at 48 h, the extent of correction tended to be greater in the animals with neurological dysfunction. The brains of the 12 corrected rabbits showed neither gross nor microscopic lesions.

## DISCUSSION

Severe hyponatraemia can result in morbidity and mortality (Lipsmeyer and Ackerman, 1966; Raskind, 1974; Arieff *et al.*, 1976; Arieff and Schmidt, 1980; Ashraf *et al.*, 1981; Fraser and Arieff, 1984). The present study confirms this well known fact. Typically the metabolic encephalopathy of severe hyponatraemia is totally reversible. Some authors, however, have suggested that uncorrected hyponatraemia can cause permanent brain damage. Such papers are unconvincing for several reasons. First, these writings deal primarily with patients who received treatment with hypertonic saline, and do not consider the possibility that the therapy itself might be injurious. Secondly, pathological examination is missing or incomplete in many of these cases (Lipsmeyer and Ackerman, 1966; Arieff and Schmidt, 1980; Ashraf *et al.*, 1981). Autopsies have been performed on patients dying with acute or chronic untreated hyponatraemia and on experimental animals dying with water intoxication. These pathological studies reported either

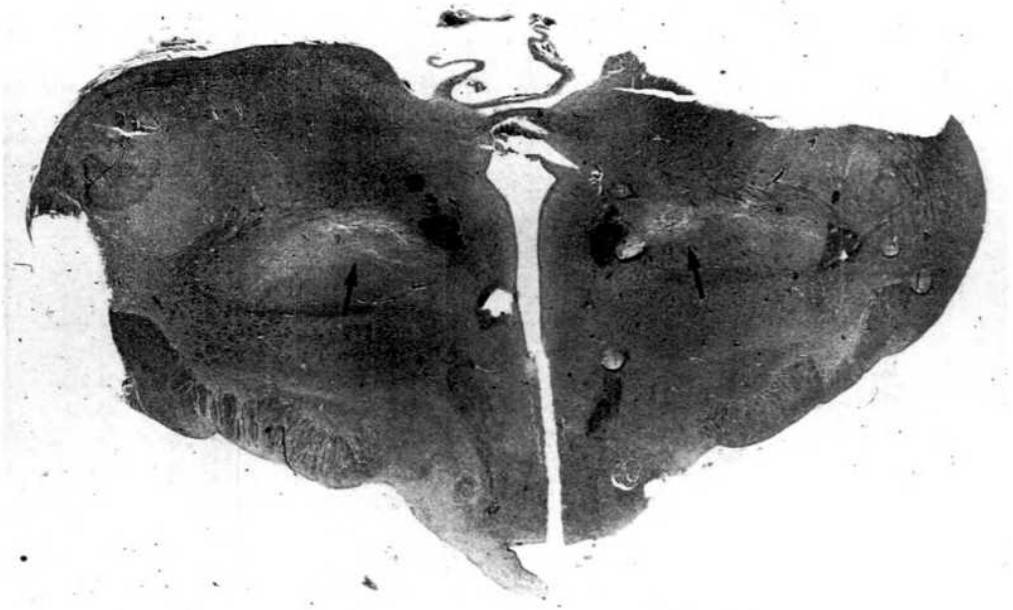
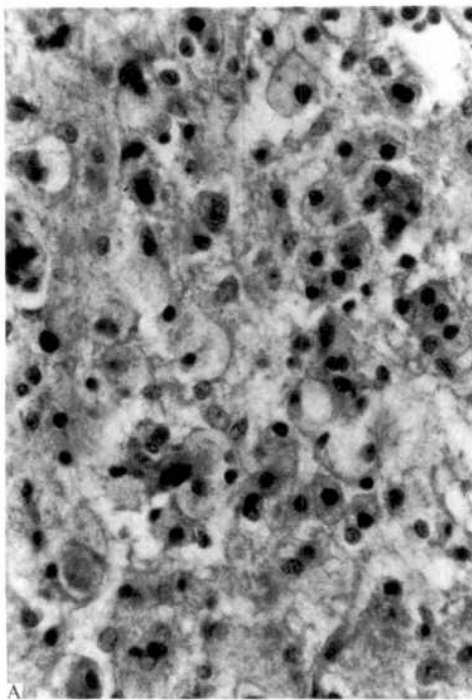
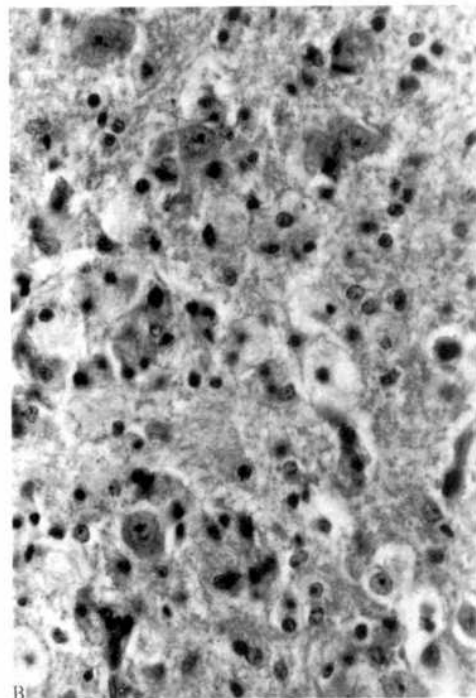


FIG. 1. Myelinolysis in the rabbit. Arrows indicate symmetric lesions in the thalamus.



A



B

FIG. 2. Microscopic views of a thalamic lesion. A, necrotic neurons and reactive change with abundant macrophages. B, more peripherally in the lesions there are macrophages in the presence of normal neurons.

TABLE 3. RABBITS WITH BRIEF<sup>1</sup> SEVERE<sup>2</sup> HYPONATRAEMIA: RAPIDLY CORRECTED (GROUP III)

| Before correction |                                        |                | After correction                       |                                                   |                              |              |
|-------------------|----------------------------------------|----------------|----------------------------------------|---------------------------------------------------|------------------------------|--------------|
| Rabbit no.        | [Na <sup>+</sup> ] mmol/l <sup>3</sup> | Signs          | [Na <sup>+</sup> ] mmol/l <sup>4</sup> | Signs <sup>5</sup>                                | Survival (days) <sup>6</sup> | Myelinolysis |
| 36                | 108                                    | Well           | 130/(138)                              | Well                                              | Killed                       | Absent       |
| 37                | 116                                    | Well           | 136/(151)                              | Well                                              | Killed                       | Absent       |
| 38                | 95                                     | Well           | 125/(148)                              | Well                                              | Killed                       | Absent       |
| 39                | 110                                    | Well           | 132/(148)                              | Well                                              | Killed                       | Absent       |
| 40                | 70                                     | Well           | 136/(143)                              | Well                                              | Killed                       | Absent       |
| 41                | 105                                    | Well           | 123/133                                | Well                                              | Killed                       | Absent       |
| 45                | 108                                    | Well           | 131/143                                | Well                                              | Killed                       | Absent       |
| 46                | 114                                    | Well           | 122/124                                | Well                                              | Killed                       | Absent       |
| 47                | 114                                    | Well           | 122/149                                | Spastic diplegia (1)                              | 2                            | Absent       |
| 48                | 110                                    | Weak, seizures | 143/153                                | Flaccid L rear leg (1), quadriplegia/lethargy (2) | 3                            | Absent       |
| 50                | 113                                    | Weak           | 128/130                                | Flaccid front legs (2)                            | 3                            | Absent       |
| 52                | 109                                    | Weak           | 140/150                                | Weak L rear leg (1), generalized weakness (2)     | 3                            | Absent       |

<sup>1</sup> Severe hyponatremia for <24 h. <sup>2</sup> [Na<sup>+</sup>] ≤ 122 mmol/l. <sup>3</sup> [Na<sup>+</sup>] immediately before correction. <sup>4</sup> [Na<sup>+</sup>] attained 24 h after treatment with hypertonic saline/[Na<sup>+</sup>] attained 48 h after treatment with hypertonic saline. Parentheses indicate that a 48 h measurement is not available; the number given is the next available measurement. <sup>5</sup> Number in parentheses indicates the day after correction on which the neurological signs were first observed. <sup>6</sup> Number of days rabbits survived after correction of hyponatraemia. Animals were killed at 21 days.

no changes in the CNS or diffuse cerebral oedema on gross examination; there can be widespread vacuolization and astrocytic swelling on microscopic examination (Rowntree, 1923; Helwig *et al.*, 1935; Lipsmeyer and Ackerman, 1966; Rymer and Fishman, 1973; Arieff *et al.*, 1976; Arieff and Schmidt, 1980; Ashraf *et al.*, 1981). No focal or myelinolytic lesions have been found in any brain.

Further data are provided by the animals with uncorrected hyponatraemia which are the controls in dog and rat studies of myelinolysis (Laureno, 1980, 1981, 1983; Kleinschmidt-DeMasters and Norenberg, 1981a; Ayus *et al.*, 1985c). Myelinolysis did not occur in any of these animals, whose hyponatraemia was sustained for only three or four days before killing or death. The Group I rabbits reported here experienced severe symptomatic hyponatraemia which was sustained for at least

seven days without correction; in half of these animals the uncorrected hyponatraemia was sustained for at least nine days. None of the rabbits developed gross or microscopic brain lesions. These data with hyponatraemia, much more prolonged than in any previous study, greatly strengthen the clinical and experimental evidence that uncorrected hyponatraemia itself does not cause myelinolysis or any other fixed brain lesions.

In contrast to rabbits with protracted uncorrected hyponatraemia, animals with only three days of severe hyponatraemia did develop myelinolysis following hypertonic saline treatment. Although both groups experienced hyponatraemia of similar severity, lesions were seen in 3 out of 7 corrected rabbits (Group II) but in none of 8 rabbits surviving for at least seven days with severe hyponatraemia (group I). This difference is statistically significant ( $P=0.07$  by Fisher's exact test). It is important to note that the serum sodium concentration rose only to low normal levels, without overcorrection, in the Group II rabbits.

All 3 animals with lesions had bilateral thalamic involvement; only 1 showed a central pontine lesion. This distribution of lesions is similar to dogs which also develop extrapontine lesions more often than pontine lesions (Laureño 1980, 1981, 1983). Rats show prominent myelinolysis in the thalamus and striatum without pontine involvement (Kleinschmidt-DeMasters and Norenberg, 1981b; Ayus *et al.*, 1985c). In humans, however, the pons is the most frequent site of myelinolytic lesions. Other reported sites of demyelination in man (deep cortical levels, cerebellum, red nucleus and striatum) were not involved in rabbits. Histologically the lesions seen in rabbits resemble those in other experimental animals and in humans with this disease: symmetric demyelination, loss of oligodendrocytes, relative preservation of neurons in the periphery of the lesions and absence of inflammation on a background of swollen astrocytes and macrophages. There was neuronal necrosis in the central areas of the lesions.

For several reasons, the brain lesions in the rapidly corrected animals cannot be attributed to hypoxia. First, there was no apparent hypoxia; seizures were rarely observed and there were no evident cardiorespiratory difficulties. Secondly, the distribution of the neuropathological lesions is unlike that of typical anoxic encephalopathy which affects the hippocampus prominently or delayed anoxic encephalopathy where the hemisphere white matter is affected. Thus the brain pathology in these animals can only be related to the shifts of serum sodium which the animals experienced.

In addition to the neuropathological changes, there was clinical evidence of neurological disease following hypertonic saline treatment. The neurological signs usually developed one to four days after the rapid correction of hyponatraemia. Each rabbit was clinically *worse* with an improved serum sodium level than it had been while markedly hyponatraemic (Table 2). For example, 4 of the 7 Group II rabbits were tremulous and 'jittery', a finding absent during uncorrected hyponatraemia. Six of these 7 animals developed severe weakness which had not been present before correction. On the other hand, 50% of rabbits with protracted

hyponatraemia did not have severe weakness. Corrected animals were also more likely to have focal symptoms, while weakness in hyponatraemic rabbits was usually generalized. The corrected animals with definite myelinolysis at autopsy showed severe weakness in all cases. This paralysis with accompanying rigidity and hyperexcitability resembles the weakness seen in dogs with CPM (Laureno, 1983).

There appears to be a general correspondence between the degree of change in serum sodium concentration at 24 and 48 h (i.e., the rate of change) and the severity of and latency to the development of symptoms. Thus a larger increase in the serum sodium concentration over 24 to 48 h (i.e., a faster rate of correction) seems to be associated with the earlier onset of symptoms of greater severity than that seen with more gradual correction. This correlation was also suggested by retrospective studies in humans (Wright *et al.*, 1979; Norenberg *et al.*, 1982; Sterns *et al.*, 1986) and has been seen in experiments on dogs and rats (Laureno, 1980; Ayus *et al.*, 1985c).

It has been suggested that the duration of hyponatraemia before correction may be a risk factor for the development of CPM (Laureno, 1980; Norenberg and Papendick, 1984). The Group III animals were severely hyponatraemic briefly (less than 24 h) before receiving hypertonic saline. Clinical symptoms of spastic diplegia, quadriplegia and lethargy were seen in 4 out of 12 animals following correction but lesions were seen in none. All the symptomatic animals died within three days of treatment. It is possible that some of these animals would have developed detectable lesions had they survived longer. The morbidity in rabbits corrected after a brief period of hyponatraemia was less than that for animals corrected after sustained hyponatraemia (33% versus 100%). Thus it appears that the rapid correction of relatively acute hyponatraemia entails the risk of neurological disease which is substantial but less than that consequent upon rapid correction of protracted hyponatraemia.

Many physicians already counsel caution in correcting severe hyponatraemia rapidly. However, their concern usually focuses on congestive heart failure, pulmonary oedema, or cerebral haemorrhage. Standard recommendations for the treatment of symptomatic hyponatraemia currently include the infusion of hypertonic saline over 8 to 12 h in order to raise the serum sodium concentration to the mildly hyponatraemic range of 125 to 130 mmol/l (Hantman *et al.*, 1973; Arieff *et al.*, 1976; Andreoli, 1982; Ayus *et al.*, 1983; Levinsky, 1983; Narins, 1986). The experiments presented here, taken together with previous studies, suggest that such guidelines may not be cautious enough. Of the 3 rabbits with myelinolysis in this study, 2 had been corrected only to 132 mmol/l within 24 h. These results demonstrate that correction to a mildly hyponatraemic state is sufficient to produce myelinolysis. In other words, rapid correction of hyponatraemia over 24 h without over-correction carries neurological risk.

Difficulty in controlling the extent of correction in a given individual is another reason for caution in prescribing saline. In the present studies on rabbits, an amount of hypertonic saline calculated to raise the serum  $[Na^+]$  to 130 mmol/l was

administered; at 24 h this treatment resulted in an average serum  $[Na^+]$  close to the target level for each population studied ( $127 \pm 12$  mmol/l in Group II and  $131 \pm 7$  mmol/l in Group III). However, individual measurements ranged from 100 to 143 by 24 h and without further treatment reached well into the normal range (124–153) by 48 h. Undoubtedly such variability in response to therapy also occurs in man.

These experiments demonstrate the risks involved in the administration of saline to severely hyponatraemic patients. They show that the extent of correction in an individual cannot be easily controlled. Even if such control were always possible, it is clear that a rapid rise in serum sodium concentration to a level which is still hyponatraemic can result in myelinolysis. The danger of inducing myelinolysis should be considered when formulating a plan of management for patients with severe hyponatraemia.

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# CHROMATICITY AND ACHROMATICITY

## EVIDENCE FOR A FUNCTIONAL DIFFERENTIATION IN VISUAL FIELD DEFECTS

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### SUMMARY

In the visual field defects of 10 patients who had suffered lesions in the postgeniculate part of the primary visual projection, red-green discrimination and achromatic target detection was tested. In addition, 8 of these patients were tested for detection of red and green targets. Targets were presented on a low photopic achromatic background, so that the red and green targets differed from the background both in intensity and in wavelength, whereas the achromatic target differed in intensity only. Six patients showed evidence of discriminating between red and green targets, 5 patients could also detect the colour targets, but none could detect the achromatic one that was presented at the same retinal position. These results imply that wavelength and intensity information are treated differentially, and suggest that these patients possess residual colour-opponent channels that subserve the defective part of the visual field.

### INTRODUCTION

A lesion in the optic radiation and/or striate cortex leads to a defect in the corresponding part of the visual field (Holmes, 1918). The loss of visual function within the defective area of the visual field depends on the characteristics of the lesion (nature, extent, density, possibly age at onset, etc.); on the basis of visual perimetry, it is determined clinically as partial or complete. Patients with partial loss can experience visual sensations within the field defect (e.g., Riddoch, 1917); they provide a model for studying the vulnerability of different visual functions, often in the framework of a hypothesis of hierarchical organization (Teuber *et al.*, 1960). However, even patients with clinically complete loss who do not experience visual sensations in the area of the defect have been shown to react to visual stimulation when forced-choice techniques are used. This type of residual visual function is often referred to as *blindsight* (Weiskrantz *et al.*, 1974). Both types of residual visual function are distinguished on the basis of the patients' statements regarding their visual experiences, or lack thereof. As such statements are of necessity subject to the patients' individual criteria, and because blindsight is often

associated with a neuroanatomical model which claims that the visual midbrain projections mediate the residual performance (Campion *et al.*, 1983), in this study only the broader term *residual visual function* will be used. Nevertheless, all patients described here claimed that they could never see the test stimuli while fixating the central fixation spot.

A wide range of residual functions has been tested in previous investigations. They include pupil reaction to global light changes in clinically anopic patients (Brindley *et al.*, 1969) as well as localization of targets presented at various positions within the 'blind' area (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1975, 1978; Barbur *et al.*, 1980; Zihl, 1980). In addition, residual discriminability, as opposed to detection, has been described, for example, for form (Weiskrantz *et al.*, 1974; Perenin, 1978), orientation (Weiskrantz *et al.*, 1974), movement direction (Barbur *et al.*, 1980), target displacement (Blythe *et al.*, 1986), and colour (Bender and Krieger, 1951).

In spite of the body of data of which only examples are given above, the extent and nature of residual vision remains controversial. Especially the more complex functions are still in dispute. One of these is colour discrimination, either between different hues or between chromatic and achromatic stimuli. Evidence for residual wavelength processing after retrogeniculate lesions was described by Bender and Krieger (1951). In contrast, Perenin *et al.* (1980) found no such evidence, and Barbur *et al.* (1980) reported that the photopic spectral sensitivity curve they had measured with a moving target was shifted towards the lower wavelengths where it coincides with the scotopic sensitivity curve, indicating rod-dominated processing. Contradictory results are also found in the literature on residual wavelength processing in nonhuman primates: Schilder *et al.* (1972; *see also* review by Pasik and Pasik, 1982) and Keating (1979) reported that their 'destriate' monkeys process wavelength information; Klüver (1941), Weiskrantz (1963) and Humphrey (1974) found no such evidence, although the results with Humphrey's monkey 'Helen' indicate that a red target has more 'salience' than a green one, implying that wavelength is a preference-influencing factor. Klüver (1941), like Leporé *et al.* (1975), reported a Purkinje-shift for photopic spectral sensitivity, whereas the results of Keating (1979) did not contain evidence for such a shift.

At least partly, such discrepancies can be accounted for by the number of intervening variables: the differences in methodology and experimental parameters render comparisons, both within and more so between species, difficult. This is particularly evident with respect to the extent and completeness of the lesion in man. In addition, the subjects' age at the onset of the lesion could influence the results, perhaps as a result of the compensatory plasticity in a younger system. In children (*see* Perenin and Jeannerod, 1975, 1978; Barbur *et al.*, 1980), or even in young adults (Damásio *et al.*, 1975), comparable lesions seem to produce milder deficits, at least with respect to certain residual visual functions. Together, these and other factors prevent the formulation of a generally accepted catalogue of residual visual functions in primates.

To promote comparability in this study, the functions were tested with a group of 10 patients. They were tested for red-green discrimination, and for detection of red, green, and achromatic targets. This combination was chosen in view of physiological data that show a differential treatment of information as to wavelength and achromatic intensity in the retina (Kaplan and Shapley, 1986), in the lateral geniculate nucleus (Wiesel and Hubel, 1966; De Valois *et al.*, 1977), and in cortical visual field representations (Michael, 1981; Livingstone and Hubel, 1984; Hubel and Livingstone, 1985). A differential treatment of these two types of information is also suggested by anatomical findings regarding the segregation of information-specific pathways (Perry and Cowey, 1984; Perry *et al.*, 1984; DeYoe and Van Essen, 1985; Hubel and Livingstone, 1985; Shipp and Zeki, 1985). In addition, psychophysical results showing that the contrast sensitivity functions for luminance and wavelength modulated gratings differ substantially, for example, with respect to high and low frequency cut-off (Mullen, 1985), may reflect this differentiation perceptually.

## PATIENTS AND METHODS

Ten patients with homonymous hemianopia or quadrantanopia participated with informed consent in the experiments. With one exception (Case 8: severe craniocerebral trauma) they had suffered vascular lesions in the territory of the posterior cerebral artery. The infarcts involved the optic radiation and the primary visual cortex; the extent and density of the lesions varied between subjects according to the CT scans used to determine their nature and location (*see* Table 1). Five patients (Cases 1–3, 8, 10) had already participated in experiments on the detection of achromatic targets (Stoerig and Pöppel, 1986). The time between the cerebral vascular lesions and the experiments ranged from six months to five years. All patients were tested on the Farnsworth-Munsell 100 hue test (Farnsworth, 1943) before the colour discrimination experiments and, within their functional visual field, showed normal trichromatic colour vision.

### *Visual Field Measurement*

Both static and dynamic perimetry was performed under monocular viewing conditions using a Tübinger perimeter (Sloan, 1971). The patients fixated a central red fixation spot with a diameter of 10 min of arc and 20 cd/m<sup>2</sup> luminance; background luminance was set at a low photopic level (3.2 cd/m<sup>2</sup>). Chin and forehead were supported, and fixation was monitored through a built-in telescope. For dynamic perimetry, a circular target (44 min, 320 cd/m<sup>2</sup>) was moved slowly (2–3 degs/s) from the far periphery towards the fixation point. The patients were instructed to press a button as soon as the target appeared within their visual field. This position was registered, and the procedure was repeated in a random sequence along the other meridia until the visual field was mapped. The resultant plots are given for the eye with the defect in the temporal visual field because this eye was used to test the residual visual functions described below (fig. 1).

In addition, incremental thresholds were measured with a descending method of limits (target: 44 min, achromatic; presentation time: 200 ms). The patients, while fixating the central red fixation point, pressed a button whenever they could distinguish the tachistoscopically presented target from the background. In 1 deg steps, this procedure was repeated three times for each retinal position on the meridian used for further experimentation (fig. 2).

TABLE 1. PATIENTS\*

| Case | Age at onset of defect (yrs) | Side      | Nature of lesion       | Localization                    |
|------|------------------------------|-----------|------------------------|---------------------------------|
| 1    | 66                           | R         | Vascular               | OR, area 17                     |
| 2    | 66                           | L         | Vascular               | OR, area 17                     |
| 3    | 44                           | L         | Vascular               | OR, area 17 and adjacent cortex |
| 4    | 50                           | L         | Vascular               | Area 17                         |
| 5    | 21                           | L         | Vascular               | Unclear                         |
| 6    | 52                           | L         | Vascular               | OR, area 17                     |
| 7    | 20                           | R         | Vascular               | Area 17                         |
| 8    | 42                           | L         | Traumatic              | OR (temporal)                   |
| 9    | 33                           | L         | Vascular               | OR, area 17 and adjacent cortex |
| 10   | 64                           | Bilateral | Vascular<br>(multiple) | Area 17 (L); OR, area 17 (R)    |

\* The table gives short descriptions of the patients' lesions based on CT scans. In the scans of Case 5 the lesion responsible for the visual field defect was not evident. Scans were not available for Case 7 and the description is based on the radiologist's report. OR = optic radiation; L = left; R = right.

#### *Procedure for Testing Residual Colour Discrimination*

Seated at the perimeter, the patients fixated the central fixation spot with the eye contralateral to the lesion. The other eye was covered with a patch; the chin and forehead were supported by rests that allowed adjustment of head and eye position; with a built-in telescope that was fitted with a reticule fixation could be controlled from the examiner's side, and the stimuli were presented when the pupil was centred on the reticule. The majority of the patients, especially Cases 1-3, 7, 8, and 10, were highly trained observers, and well motivated; their fixation was very good. Background luminance was set at a low photopic level ( $1.6 \text{ cd/m}^2$ ); its colour temperature, according to the manufacturer (Osram-bulb 7523 BA 15S), was  $2825 \pm 25 \text{ deg K}$ . The sound-proof room where the perimeter stood was illuminated only by a dim light on the experimenter's side.

Depending on each patient's preference, the achromatic fixation point was 10 or 30 min in diameter. When the patient fixated this point, circular visual targets (44 min) that appeared green and red, respectively, were successively presented for 200 ms. The coloured targets were produced by inserting filters into the achromatic projection beam that provided the target. The green target was a bandpass filter with a peak at 505 nm and a half-width of 30 nm. The red one was a high-pass filter with a low cut-off at 620 nm; with a linear slope, it reaches its maximum at 660 nm. The luminances that are given for targets, background, and fixation point were measured with a Pritchard photometer (type 1980A): colour targets:  $10 \text{ cd/m}^2$ ; background:  $1.6 \text{ cd/m}^2$ ; fixation point:  $32 \text{ cd/m}^2$ .

The retinal position to be tested was individually selected according to each patient's area of blindness. First, to avoid cues from stray light, this position had to lie well within the field defect. Second, at the mirror-symmetric position (about the vertical meridian) in the functional half-field, red-green discrimination had to be flawless under the same experimental conditions. To trigger a response, each presentation was accompanied by an auditory signal, and the patients were asked to guess every time they heard this signal whether the target had been red or green. Red and green targets were presented in random sequence. Up to 200 presentations were given in one series; at the beginning of each series the targets were presented 10 times, and the examiner said which was which. After each series, the patient was asked whether he or she had seen or felt anything related to the stimulus presentation. They consistently said they had not perceived anything but the fixation point, and were only guessing. During the rest period between different series, the experimenter told the

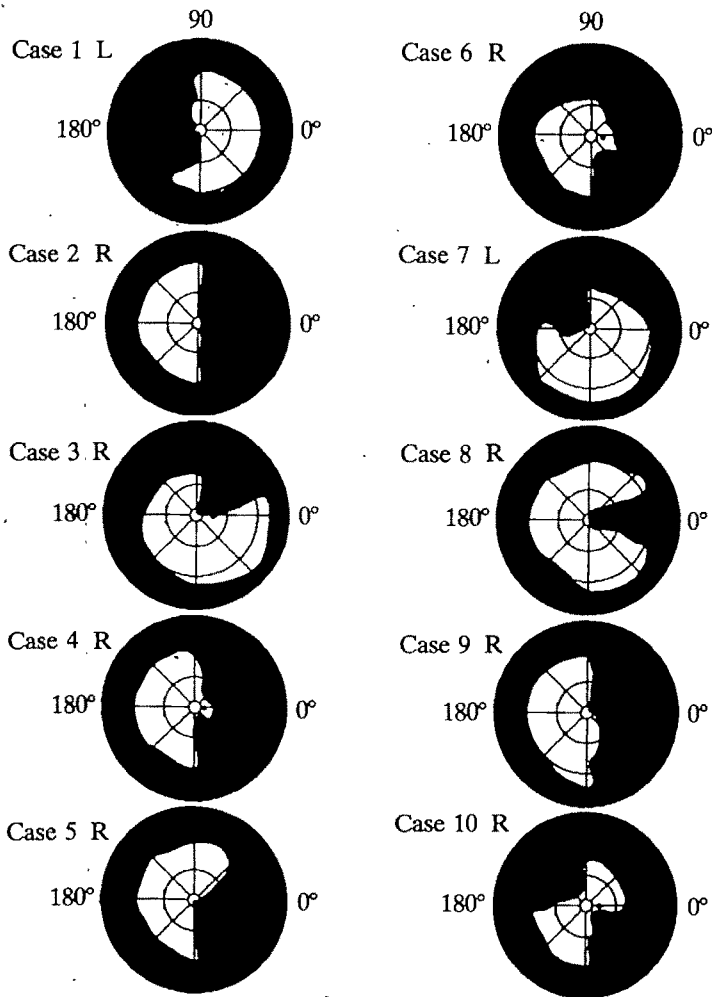


FIG. 1. The visual fields of the patients mapped perimetrically with an achromatic target of 44 min diameter and 320 cd/m<sup>2</sup> luminance. The white parts correspond to the functional visual field. The outermost circle indicates 90 deg eccentricity from the fixation point, whereas the more central circles indicate 10, 30, and 60 deg eccentricity, respectively. In each case, the visual field with the defect on the temporal side is shown.

patients whether they had performed 'very well', 'alright,' or 'not as well as before'; they were never told they had performed at chance level.

To derive a reliable discriminability index, analogous to the Receiver-Operating-Characteristic (ROC) curves measured in the detection experiments (*see below*), a response curve was determined by varying the ratio between the discriminanda. This ratio, which indicates the probability of occurrence of red and green targets, was varied for those 6 patients whose health allowed the necessarily prolonged testing. Five ratios of red versus green targets were then used (1:4, 1:2, 1:1, 2:1, 4:1). To shift their decision criteria, before each experiment the patients were informed about the ratio. This is also true for the remaining 4 patients who were only tested in the condition where red and green stimuli were equally likely to appear (1:1).

For each ratio, every patient was given 500 presentations; their answers were registered in relation to the actual condition, leading to four-field matrices (red/green, red/red, green/red, green/green)

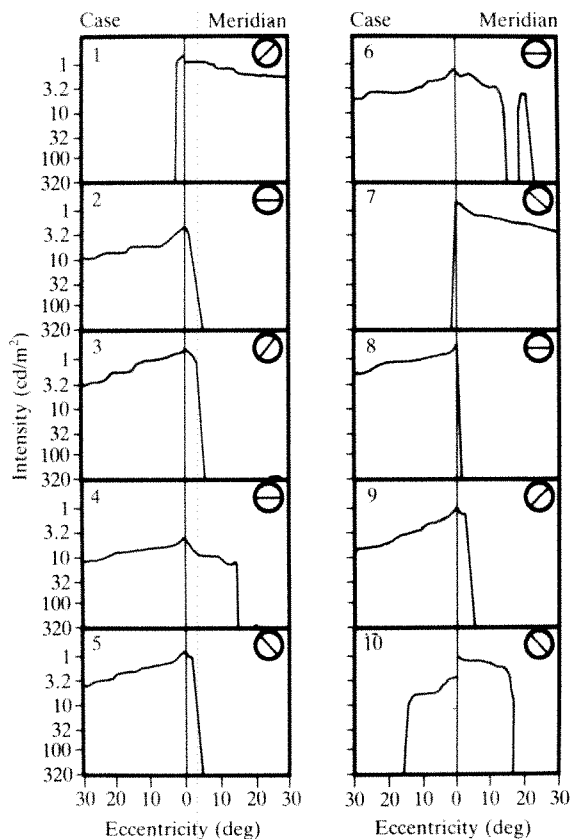


FIG. 2. Incremental thresholds measured with an achromatic 44 min target along the meridian used for further testing. For each patient, this meridian is indicated in the circle inserted in the upper right corner.

that were used to calculate the percentages of correct and incorrect answers, as well as the  $\chi^2$  values. By analogy with the ROC curves measured for the target detection tasks, the conditional probabilities  $P(\text{green/red})$  and  $P(\text{green/green})$  were calculated for each ratio, giving a response curve for the patient's performance. The discriminability is given by the area underneath the curve to allow easy comparison with the detection data.

#### *Procedure for Testing Target Detection*

To measure residual target detection, at the retinal position used for the red-green discrimination, targets were presented in random alternation with 'blanks', and the patients' task was to guess whether the target had been presented or not. Three stimuli were used: green, red, and achromatic. The intensity of the achromatic target was higher ( $16 \text{ cd/m}^2$ ) than that of the colour targets which were the same as in the colour discrimination experiment ( $10 \text{ cd/m}^2$ ). The achromatic test was subserved by a 6 V, 25 Watt bulb; according to the manufacturers, its colour temperature was  $2850 \pm 100 \text{ deg K}$ . The same achromatic target was used to test target detection at a position within the natural blind spot. When the latter lay within the field defect its position was assumed to correspond in eccentricity to that in the intact field of the other eye.

Eight patients participated in the detection tests with red and green targets. With 5 patients, ROCs were measured by varying the ratio of target to blank presentations; again, five ratios were used. In every case, 500 presentations were given for each ratio, each colour, and each retinal position; as in



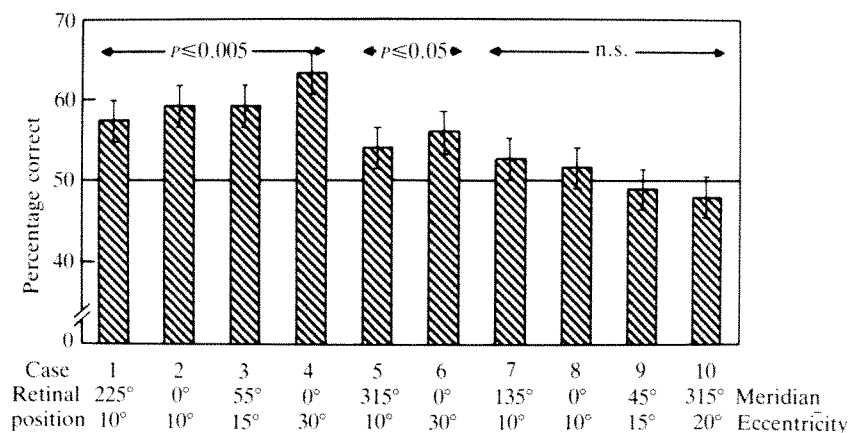


FIG. 3. The percentage correct values for 10 patients in the red-green discrimination task when red and green targets are presented equally often: 50% correct corresponds to chance performance. SEs are given, but the significance estimates given at the top are based on the  $\chi^2$  test.

the discrimination experiments, the patients were informed about the ratio. On the basis of the patients' answers, Hit Rates ( $P(1/1)$ ), False Alarm Rates ( $P(1/0)$ ), and percentage correct values were calculated, together with their standard errors (SE) that were derived from the binominal distribution. As there is a SE for both the Hit and False Alarm Rates, the larger was plotted orthogonal to the diagonal that represents chance performance. When ROCs were traced out, the area underneath the ROC was used as a single sensitivity index; it was calculated by means of the trapezoidal rule (see Stoerig *et al.*, 1985, for a detailed description of the procedure).

The testing sequence differed between patients; some were first tested on the achromatic target detection task, then on colour discrimination; for others, the sequence started with the detection of the coloured targets.

## RESULTS

### Colour discrimination

In fig. 3, the percentage correct values, together with their SEs, are given for the red-green discrimination when red and green targets were equally often presented: 50% correct corresponds to chance performance. The significance of the performance is estimated with the  $\chi^2$  test and indicated at the top of the figure, which shows that 6 out of 10 patients performed above chance in this task.

An example of the response curves obtained by varying the ratio of red to green targets is given in fig. 4. For reasons of comparability with the target detection results, the 'Hits' for the green targets ( $P(\text{green/green})$ ) are plotted against the incorrect 'red' answers under the green condition ( $P(\text{red/green})$ ); the latter correspond to false positive answers in a detection experiment. The SEs are calculated from the binominal distribution and, as the distance to the diagonal that represents chance performance is crucial, the larger one is plotted orthogonal to this diagonal. The significance of each point on the curve is estimated with the  $\chi^2$  test, and is indicated by the star-like dots.

Both response curves in fig. 4 represent the same patient's discriminability, and

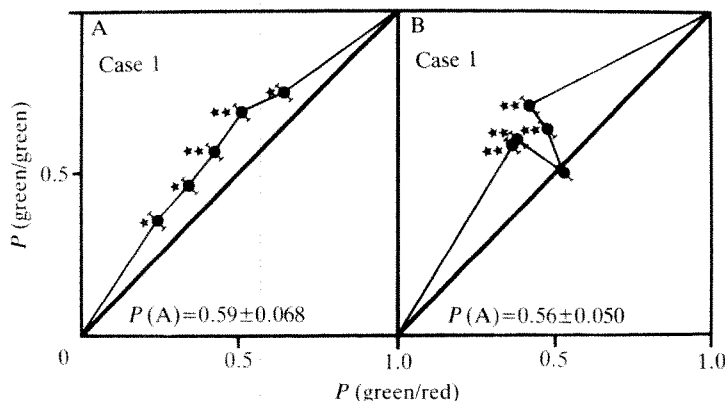


FIG. 4. The response curves represent the red-green discriminability for Case 1 as traced out by varying the ratio of red to green targets. Fig. 4A shows the data gathered with the patient being informed about the ratio used. Fig. 4B represents 'ratio-ignorant' data. The  $P(A)$  values giving the area underneath the curves are calculated by means of the trapezoidal rule. The star-like dots indicate the significance of the performance represented in each point as estimated with the  $\chi^2$  test (★:  $P=0.05$ ; ★★:  $P=0.005$ ).

were obtained by varying the ratio of red and green targets; but in contrast to fig. 4B, fig. 4A illustrates the influence of the shift in decision criterion caused by informing the subject about the ratio of red and green targets. It is obvious from fig. 4A that when the subject knows the ratio, the individual points are spaced out along the diagonal. When the ratio is not known, the subject tends to guess roughly in a 1:1 fashion, causing the data points to fall closely together.

The area underneath the curve ( $P(A)$ ) was calculated to provide a single discriminability index. Errorless performance would yield a  $P(A)$  value of 1, chance performance a  $P(A)$  value of 0.5. The confidence interval is derived by calculating the area given by the lower end points of  $1.65 \times$  the larger SE, corresponding to a one-tailed alpha of 0.05. When just one point is determined, and red and green targets have equal probability, the  $P(A)$  value is equivalent to the percentage correct value. In Table 2, the  $P(A)$  values from the colour discrimination curves are summarized. They are roughly in congruence with the percentage correct values for the 1:1 situation that are given in fig. 3.

To eliminate brightness differences, the red and green stimuli were equiluminant with respect to the normal observer's spectral luminosity function. Equiluminance was determined by using the Pritchard photometer. In addition, when asked to judge the luminosity of the stimuli in the functional visual field, the patients declared that they looked equally bright, but at the same time said this was very hard to judge, a difficulty generally experienced with heterochromatic luminosity judgements. Luminance thresholds, when measured at the corresponding retinal position in the functional visual field with the chromatic and the achromatic stimuli, varied intraindividually within a range of maximally  $0.5 \text{ cd/m}^2$ ; for instance, Case 10 could reliably detect the red target at an intensity of  $2.1 \text{ cd/m}^2$ , the achromatic one at  $2.4 \text{ cd/m}^2$ , and the green one at  $2.5 \text{ cd/m}^2$ . However, strict tests for equi-

TABLE 2. RED-GREEN DISCRIMINATION RESULTS

| Case | Eye | Retinal position<br>(meridian/eccentricity) | Area underneath curve<br>( $P(A)$ ) | No. of significant<br>points |
|------|-----|---------------------------------------------|-------------------------------------|------------------------------|
| 1    | L   | 225/10                                      | $0.59 \pm 0.068$                    | 5                            |
| 2    | R   | 0/10                                        | $0.61 \pm 0.069$                    | 5                            |
| 3    | R   | 55/15                                       | $0.62 \pm 0.070$                    | 5                            |
| 4    | R   | 0/30                                        | $0.61 \pm 0.020$                    | 1*                           |
| 5    | R   | 315/10                                      | $0.54 \pm 0.019$                    | 1*                           |
| 6    | R   | 0/30                                        | $0.56 \pm 0.020$                    | 1*                           |
| 7    | L   | 135/10                                      | $0.55 \pm 0.063$                    | 1                            |
| 8    | R   | 0/10                                        | $0.53 \pm 0.069$                    | 1                            |
| 9    | R   | 45/15                                       | $0.49 \pm 0.020$                    | 0*                           |
| 10   | R   | 315/20                                      | $0.51 \pm 0.071$                    | 0                            |

\*The results for the red-green discrimination are given by the area under the response curves ( $P(A)$ ) that are traced out by varying the ratio between red and green targets. The asterisks in the last column indicate the cases where only one such point could be determined, with equal probability for red and green targets to appear.

luminance in the functional visual field cannot ensure that the targets 'appear' equally bright in the defective visual field. If the spectral sensitivity changed following a geniculostriate lesion, causing the photopic wavelength sensitivity function to coincide with the scotopic one, as reported for the monkey (Leporé *et al.*, 1975) and the patient described by Barbur and colleagues (Barbur *et al.*, 1980), a large subjective difference in the targets' brightness would ensue. The patients could then base their decisions on this cue, without discriminating wavelength. Under this assumption, the red target ought to be subjectively darker than the green one, or even undetectable if below a 'residual detection threshold'. In the first case, what looks like a red-green discrimination would in reality be an intensity discrimination, that is, the detection of a luminance difference. In the second case, it would be a 'green versus no stimulus' discrimination, namely, a green target detection.

To control for the first possibility, 2 of the patients who had performed well above chance in the wavelength discrimination (Cases 1 and 3) were tested in an intensity discrimination. The same experimental procedure and the same retinal position were used; the targets were achromatic and the same size (44 min diameter) as before, but differed in luminance by 1 log unit (16 vs 160 cd/m<sup>2</sup>), and, consequently, in luminous flux. The patients' task was to decide on each presentation which target had been presented, and the results are given in fig. 5. Both patients performed at chance level.

According to the internationally standardized spectral sensitivity curve for the dark adapted eye, the difference in subjective luminosity between a red and green stimulus is closer to 3 log units than to 1 (Davson, 1980). However, such a large difference was not used in this control experiment because the darker stimulus used ought to lie well above the threshold value measured in the functional visual field,

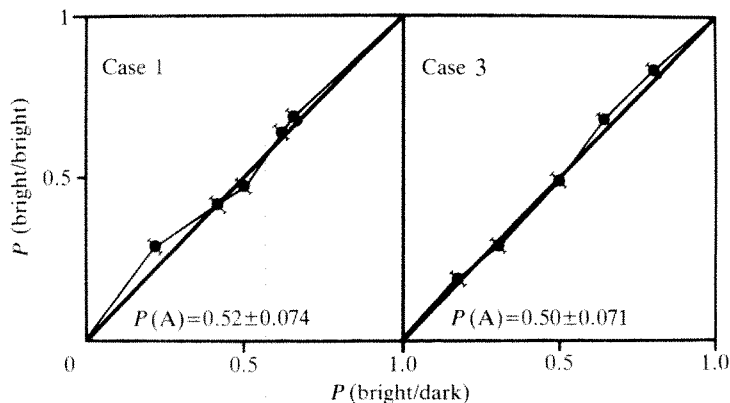


FIG. 5. The curves represent the brightness discriminability tested in 2 patients (Cases 1 (*left*) and 3 (*right*)) using 44 min achromatic targets of 16 and 160 cd/m<sup>2</sup>, respectively. The patients, although performing above chance in the wavelength discrimination task, could not discriminate between the two achromatic stimuli that differed in luminance flux.

and the brighter one, if 3 log units more intense, would emit too much stray light to exclude detectability by use of the functional visual field. If the red target really appeared that much darker than the green one, the second possibility provides a better hypothesis: if the red target fell beneath threshold, the significant results seen in the wavelength discrimination ought to be due to a 'green target detection'.

#### Target Detection

At the same retinal position, the detection of red, green, and achromatic targets was tested. The red and green stimuli were the same as before (44 min visual angle, 10 cd/m<sup>2</sup>); the achromatic one was the same size, but slightly brighter (44 min, 16 cd/m<sup>2</sup>), corresponding to the darker target used in the brightness control experiment. In fig. 6, the resultant ROCs are shown for the three target detection tasks. The Hit Rates ( $P(1/1)$ ) and False Alarm Rates ( $P(1/0)$ ) are given with the larger SE plotted orthogonal to the diagonal that represents chance performance. The  $P(A)$  values that are inserted are calculated by means of the trapezoidal rule, providing a conservative index of detectability. The error estimation is derived by calculating the area given by the lower end-points of 1.65 times the larger SE, corresponding to a one-tailed alpha of 0.05.

The results for the red target do not differ in any obvious way from those for the green target: both red and green targets yield results that are significantly above chance. This is also true for Cases 5, 6 and 9, who could only be tested in the equal probability condition (1:1). As a difference in the performance with the two colours should have been observed if the red target had, due to a Purkinje shift in spectral sensitivity, fallen into a region of low spectral sensitivity, the results do not favour the notion that the red target—the same as used in the discrimination experiments—fell below threshold. This excludes the second possible cause of an artefactual red-green discrimination. A marked contrast, however, can be seen between the

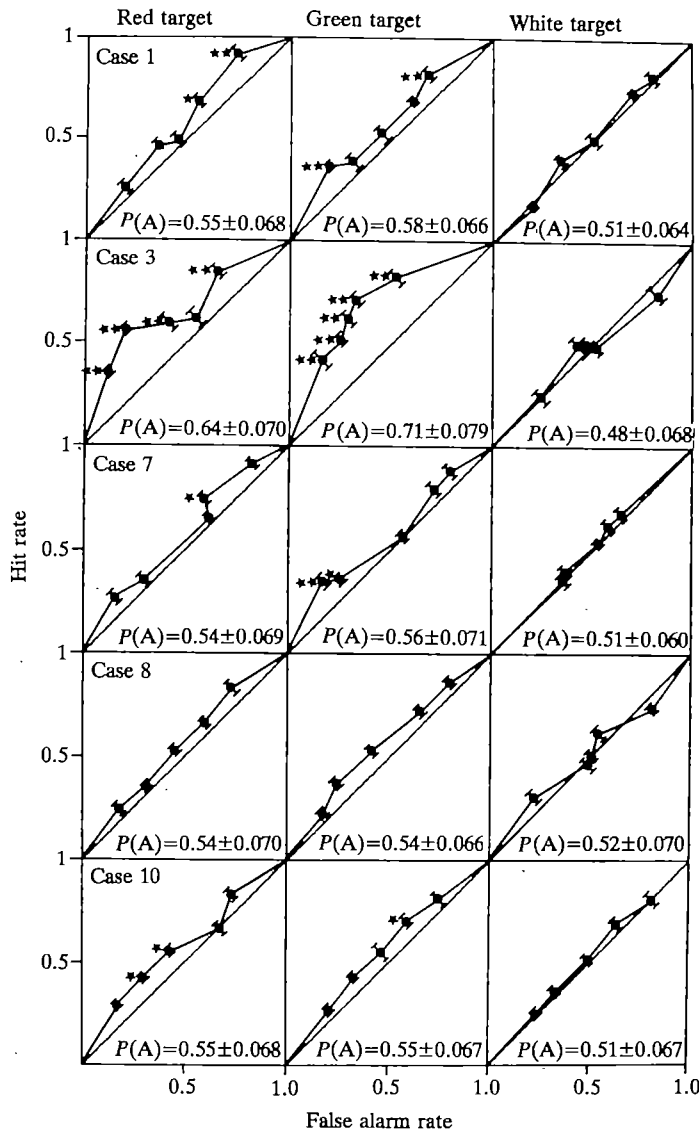


FIG. 6. Receiver-Operating-Characteristic curves for 5 patients measured with red, green, and achromatic targets by varying the ratio of target to blank presentations. The larger SE is drawn orthogonal to the diagonal that represents chance performance. In contrast to the achromatic target, the red and green targets both yield significant detectability.

performance with achromatic and red or green targets. With the exception of Case 8, there are significant points, each representing 500 individual trials, on all the ROCs that represent the detectability of the coloured targets. On the ROCs representing the detectability of the achromatic target, however, not a single ROC point is significant at the 0.05 level.

The ROCs measured with the achromatic target are in accordance with the

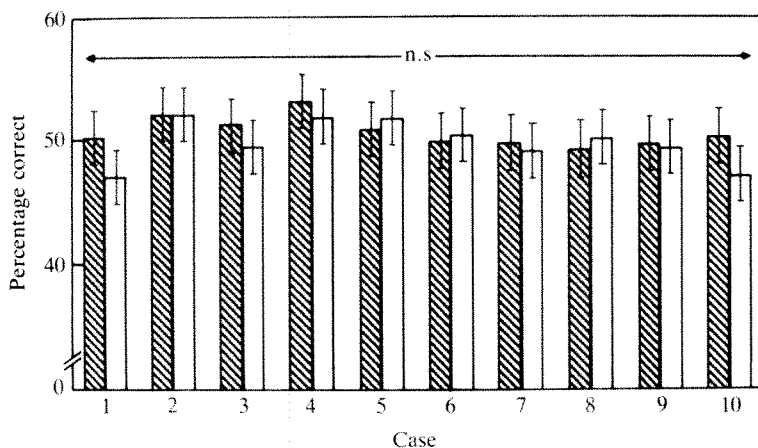


FIG. 7. The percentage correct values for the detection of the achromatic target under the 1:1 condition show that none of the patients can detect the achromatic target at the position used for testing colour discriminability. When, as a control against stray light effects, a position within the same eye's blind spot is tested, there is no detection either. Hatched area = retinal position as before; open area = blind spot.

results of the 4 patients who could only be tested in a 1:1 condition. To ensure comparability with fig. 3 (red-green discrimination), the results for the 1:1 ratio are given in fig. 7. It can be seen that the data strongly resemble those gained from testing in the blind spot, a retinal position that was included in the experiments to provide a control against artefacts from light scatter. (ROCs measured at positions within the blind spot have previously been published (Stoerig and Pöppel, 1986).)

In view of these data it is interesting to note again the lack of detectability with a luminance difference of 1 log unit seen in the control experiment (*see* fig. 5). Obviously both achromatic targets were undetectable, and the lack of detectability for the achromatic target could not be overcome by a tenfold increase in intensity; otherwise a discrimination—actually due to a detectability of the brighter target—should have been observed.

Our previously published data show that the detectability of an achromatic target depends on the eccentricity of the retinal position tested (Stoerig and Pöppel, 1986). Therefore the possibility cannot be excluded that the 2 patients whose field defects are restricted to the periphery, so that the most central retinal position that could reasonably be tested was at 30 deg eccentricity, might have shown some residual detectability for the achromatic target if a complete ROC had been traced out. In spite of this restriction, it is clear from the detection data presented in fig. 6 that it is the colour of the stimuli that makes the difference between detectability and undetectability. The targets that differ from the background in both wavelength and intensity are detected and discriminated at the relatively central retinal position under the experimental conditions described, whereas the targets that differ only in intensity are not.

## DISCUSSION

Six of the patients tested in these series give clear evidence for a residual ability to discriminate between red and green targets. The results, at least in 4 cases, are highly significant. The discriminability is unlikely to be due to a subjective difference in brightness: both red and green targets were detectable, and no discriminability for a 1 log unit intensity difference was observed in control experiments.

Apart from the residual colour processing, the most striking result, in all patients, is the lack of detectability of the achromatic target presented in the same retinal position used in the colour tasks. A learning effect that could theoretically be responsible for such a finding is empirically excluded; often the achromatic target detection was not the first function tested, and generally no time correlated improvement was observed. Taken together, the two findings imply that under these experimental conditions only the targets that differ from the background in both wavelength and intensity information are processed in a way that allows the patients to 'guess correctly' more often than chance permits. To explain this effect, an underlying neuronal substrate has to be assumed that reacts only, or better, to wavelength differences, and not, or less, to intensity information. Such characteristics have been described for colour-specific cells.

In the primate retina, the colour-specific cells form the morphologically distinguished class of P-beta ganglion cells (Perry and Cowey, 1981). The larger part of these cells have colour-opponent receptive field properties, although cells with uniform fields have also been described. The P-beta cells project to the parvocellular layers of the lateral geniculate nucleus (LGN) (Perry *et al.*, 1984), and possibly to the lateral pulvinar nucleus where a small population of colour-opponent cells has been found (Felsten *et al.*, 1983).

For luminance variations, the receptive fields of colour-opponent cells (e.g., red + /green -) are known to be antagonistically organized in a centre-surround arrangement, like the cells described by Kuffler (1953) for the cat's retina. The firing rate of such a cell reaches a maximum (or minimum) when the field centre is covered by an achromatic stimulus, and decreases (or increases) with further increases in stimulus diameter. For wavelength variations, however, colour-opponent cells in the LGN were found to show a synergistic response mode. They increase (or decrease) their firing rate with increasing stimulus area until the stimulus covers the whole of the receptive field, regardless of the centre-surround organization (Wiesel and Hubel, 1966; De Valois *et al.*, 1977). Thus, depending on the size of the stimulus, the cells respond differently to achromatic intensity and wavelength information: if the stimulus covers more than the receptive field's centre, the cells react better to changes in the appropriate wavelengths than to changes in luminance.

In view of receptive field sizes measured for these cells in the monkey (Wiesel and Hubel, 1966), and perceptive field sizes in man (Wilson, 1970; Ransom-Hogg and Spillmann, 1980), it is possible that at the position that was tested within the

field defect, the stimulus size of 44 min of visual angle exceeds the area of receptive field centre. Under normal circumstances this would not prevent the perception of an achromatic target on an achromatic background, the coverage factor being very high, and the effect of receptive field organization presumably being compensated for by interactive processes that might allow the most sensitive cell to determine threshold (e.g., Oehler, 1985). After a postgeniculate lesion, however, the severe retrograde degeneration of LGN and retinal ganglion cells (Van Buren, 1963; Cowey, 1974) might cause a function mediated by such a heavily degenerated system to depend on the functional characteristics of its few surviving cells. Under such circumstances, the lack of reactivity seen with the achromatic target could be due to the suboptimal stimulation with a target that is too large to produce an optimal response from one cell, but too small to cover the receptive fields of several cells.

The differential treatment of wavelength and intensity information in the colour-opponent LGN cells is relative, as, dependent on stimulus size, the cells react *better* to wavelength than to intensity variations. In contrast, the colour-opponent, nonantagonistic type II cells described by Wiesel and Hubel (1966) in the dorsal LGN layers show no reactivity to an achromatic target, regardless of this target's size or exact position within the receptive field. The same is true for the double-opponent cells found at the cortical level that respond exclusively to changes in the appropriate wavelengths. Double-opponent cells (e.g., red +, green - / red -, green +) have been found in striate cortex (Michael, 1981; Livingstone and Hubel, 1984), in the thin cytochrome oxidase positive stripes and interstripe zones in V2 (Livingstone and Hubel, 1984; DeYoe and Van Essen, 1985; Hubel and Livingstone, 1985), and in the 'colour area' V4 (Zeki, 1980; Shipp and Zeki, 1985). Although the extrastriate visual field representations receive their major input via V1, a projection severed in the patients who participated in this study, they could, in the absence of a functional optic radiation, still get input via the pulvino-extrastriate pathway (e.g., Chow, 1950), or via the sparse but direct projection from LGN to extrastriate areas V2 and V4 (Benevento and Yoshida, 1981; Fries, 1981; Yuki and Iwai, 1981; Bullier and Kennedy, 1983) that could be demonstrated even after ablation of V1 (Yuki and Iwai, 1981). The existence of these pathways in man is inferred from monkey experiments and, of course, the precise course they may take to their target area is not known. Should they branch off from the optic radiation, the degree of involvement of more anterior parts of the radiation (as in Case 8) may provide one possible explanation for the difference between the patients who perform above chance, and those who do not. An alternative explanation is provided by the presumably small coverage factor that is caused by retrograde degeneration in the LGN; a stimulus might fall into a portion of the visual field that is not sufficiently covered to allow reactivity. This, however, remains speculative, and many other factors, including the degree of destruction in the optic radiation and in V1, may play a part.

In the monkey, neurons that respond selectively to wavelength information have



not been found in the retinomesencephalic pathways: both the superior colliculus and the pretectal area receive their retinal input from ganglion cells that are either broadband P-alpha cells, or belong to the heterogenous class of P-gamma cells (Perry and Cowey, 1984). The colour-opponent P-beta cells do not project to the midbrain (Perry *et al.*, 1984) whose colour processing properties are restricted to a rather nonspecific spectral tuning (Wolin *et al.*, 1966; Kadoya *et al.*, 1971) as opposed to colour opponency. This pathway has often been invoked in studies on residual visual functions (e.g., Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1975; Barbur *et al.*, 1980; Zihl, 1981), but it makes an unlikely candidate for residual wavelength processing: even if this tuning were sufficient for a discrimination of wavelengths that, like red and green, are far apart (as suggested by Keating, 1979), the specific lack of detectability for an achromatic target is not in accordance with the known physiological properties of the midbrain structures.

Collectively, these arguments suggest some residual colour-opponent processing within the retinothalamic pathways that subserve the defective visual field, and possibly double-opponent mechanisms in cortical visual field representations. They have several implications that may allow further specification. If, for instance, this lack of detectability for the achromatic target were due to the functional properties of type II cells that do not react to achromatic stimuli presented on an achromatic background, a reduction in the size of the achromatic target should make no difference to the patients' performance. In contrast, were the lack of detectability of the achromatic target due to suboptimal stimulation of colour-opponent cells with antagonistic organization, the size of the achromatic target should be crucial for its detectability. Reducing this size until it roughly matches the size of the receptive field centre for achromatic targets should improve detectability.

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## RESIDUAL VISION IN PATIENTS WITH RETROGENICULATE LESIONS OF THE VISUAL PATHWAYS

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### SUMMARY

Twenty-five subjects have been studied who, as a result of damage to the striate cortex, were 'blind' in extensive areas (scotomata) of the visual fields. Of these 25 subjects, 5 exhibited residual vision in response to transient lights presented within the scotoma, which enabled them to locate the stimuli by hand-reaching or by eye movements; the latter have been measured by electro-oculography. The residual vision underlying their responses was characterized by low flicker-fusion and by sensitivity in detection of movement which increased as target speed was raised. Discrimination for the direction of target movement was poor, but spatial resolution in the discrimination of target displacement was essentially normal. The subjects were unable to recognize or discriminate the spatial structure of targets located within the 'blind' field, and the observed dissociation between spatial discrimination of displacement and pattern is examined in relation to the 'two systems' hypothesis of visual function. There is no obvious correlation between the extent of neuronal damage as revealed by CT scans and the existence of residual vision.

### INTRODUCTION

Visual field losses caused by damage to the striate cortex are usually absolute (Holmes, 1918; Teuber *et al.*, 1960), but Riddoch (1917) reported that in some cases, flashed or moving lights located within 'blind' areas of the visual field can be detected. Renewed interest in the nature of visual deficits produced by cortical lesions was stimulated by reports that recovery of visual function occurs in non-human primates following ablation of the striate cortex (Pasik and Pasik, 1971; Weiskrantz, 1972). Such recovery requires that the animals receive training in visual discrimination tasks (Cowey, 1967), and was thought not to occur if both striate and prestriate cortical areas are damaged (Pasik and Pasik, 1971). Subsequently, however, residual vision has been observed in monkeys suffering damage of both striate and prestriate areas (Keating, 1979, 1980; Pasik and Pasik, 1982).

There are a number of nonstriate retinal projections which could mediate visual functions in the absence of the primate striate cortex, including those to the superior

colliculi and accessory optic tracts, and the sparse direct projections from the dorsal lateral geniculate nuclei to the prestriate cortex. The major nongeniculate projection from the retina is to the superior colliculi and here the visual field is mapped topographically onto the superficial layers. Neurons in these layers respond selectively to flashed and fast-moving targets (Schiller and Koerner, 1971; Cynader and Berman, 1972; Goldberg and Wurtz, 1972). The superior colliculus projects via the pulvinar to the prestriate cortex, and experiments on animals with ablation of either the superior colliculus or the striate cortex suggest the parallel operation of two qualitatively different visual pathways. According to this 'two systems' theory of visual organization, the striate projection mediates discrimination of detailed stimulus parameters such as spatial pattern, whereas the collicular pathway controls eye movements made in response to light stimuli (Sprague, 1966; Schneider, 1969; *see also* Trevarthen, 1969). Subsequently, Mohler and Wurtz (1977) have shown in the macaque that recovery of visual functions occurs if either the superior colliculus or the striate cortex alone is damaged, but damage to corresponding regions of both brain areas leads to permanent impairment of visual function. Thus experiments on nonhuman species demonstrate considerable flexibility in the organization of function following damage to visual centres in the brain.

In man, Pöppel *et al.* (1973) reported visual localization of targets presented within the 'blind' hemifield of 4 hemianopes, and Weiskrantz *et al.* (1974) observed a variety of visual discriminations under 'forced choice' conditions, including that between spatial patterns, for targets presented to the 'blind' hemifield of their patient D.B. D.B. denied his ability to discriminate targets presented to his 'blind' visual hemifield, the stimuli eliciting no visual sensation. This ability to locate and discriminate between visual stimuli in the absence of conscious sensation was termed 'blindsight', and other cases in which subjects could locate objects presented within 'blind' visual field areas were reported by Perenin and Jeannerod (1978), Zihl (1980) and Bridgeman and Staggs (1982). Responses to light stimulation of 'blind' visual field areas were also shown to improve with repetition of the visual task (Zihl and von Cramon, 1979).

The response characteristics for visual detection of stimuli presented within the 'blind' right hemifield of a subject G.Y., who also took part in the study to be described, were extensively investigated by Barbur *et al.* (1980). G.Y. detects a 'dark shadow' in response to transient stimulation of his 'blind' hemifield and the characteristics of this residual vision suggested activity in the retinocollicular pathway. Thus the term 'blindsight' refers to those functions occurring when the subject has no conscious awareness of them, whereas in residual vision, some conscious percept is registered. Both groups of subjects have damage to the retro-geniculate pathway, and as both are able to localize transient stimuli presented within scotomata, it seems probable that they are expressions of similar neural activity. They may, therefore, reflect differences in degree of responsiveness, but the possibility that they represent completely independent neuronal activities cannot be excluded. Previous studies of residual vision have been restricted to single cases or

small groups, but this report is based on a survey of 25 subjects who have sustained varying degrees of damage to the retrogeniculate visual pathway as revealed by computer tomographic (CT) x-ray scanning and, consequently, have extensive visual field losses.

The possibility that 'blindsight' and residual visual function in hemianopes is caused by light scattered into the normal field has recently been discussed (Campion *et al.*, 1983), but a number of experiments (Barbur *et al.*, 1980; Barbur and Ruddock, 1983; Weiskrantz, 1983; Zihl and Werth 1984; Stoerig *et al.*, 1985) have demonstrated that it cannot generate the observed responses.

### SUBJECTS AND METHODS

Twenty-five patients who had sustained damage to their retrogeniculate visual pathways were examined. There were 18 male and 7 female subjects of mean age 50 yrs (range 27–74). Clinical details of the 25 patients are provided in Table 1. The aetiology of the lesion in the majority (80%) was cerebral infarction in the territory of the posterior cerebral artery. In the remainder, 2 patients had sustained a closed head injury, 1 a middle cerebral artery infarction at birth (Case 23), 1 an occipital lobe haematoma, 1 an occipital lobectomy for a glioma, and 1 a large posterior arteriovenous malformation. None of the patients demonstrated any neuropsychological disturbance such as aphasia or memory disturbance. Neuro-ophthalmological examination failed to reveal any disturbance of eye fixation or saccadic eye movements.

The extent to which the patients' visual field abnormality resulted in a functional disturbance varied. Some patients complained of difficulty in avoiding obstacles located on the side of their field defect or of difficulty in reading. These disturbances did not show any correlation with the size of the visual field defect.

#### *Visual Field Mapping*

The visual field defect of each patient was plotted using a standard Goldmann perimeter. During visual field measurement, the patient fixated a central fixation point. One eye was covered and the head was supported by a chin and forehead rest; fixation was monitored through a built-in telescope. Measurements were made for both large ( $V = 64 \text{ mm}^2$ ) and small ( $II = 1 \text{ mm}^2$ ) circular targets (luminance  $320 \text{ cd/m}^2$ ) moving at 2 to 3 deg/s from the periphery towards the centre, against a background illumination of  $3.2 \text{ cd/m}^2$ . The subject pressed a button as soon as the target was detected, at which time the position of the target was registered and the procedure repeated for a number of different meridians. Examples of the resulting visual fields so determined are shown in fig. 1.

#### *Saccadic Localization*

The patients' eye movements were recorded using d.c. electro-oculography. Chlorided silver electrodes were applied to the skin medial and lateral to the inner and outer canthi, respectively, of one eye, and a ground electrode placed on the forehead. The corneoretinal potential was amplified and displayed on paper by an inkjet rectilinear recorder. The subject was seated 75 cm from a display containing 9 light-emitting diodes (LEDs) each separated by  $7.5^\circ$  arranged along the horizontal meridian giving a total range of  $\pm 30^\circ$ . Each LED emitted green light with peak wavelength of 565 nm, was of luminance  $5.6 \text{ cd/m}^2$  and subtended 23 min at the subject's eye. After the subject had been dark adapted for 10–15 min, the system was calibrated and 5 runs of stimulus presentations were then performed, each run preceded by a 2 min rest and a recalibration. Each run consisted of a series of trials in which the central fixation LED was 'on' for 4 s, followed immediately by one randomly chosen peripheral LED 'on' for 100 ms. All LEDs were then 'off' for 2 s, and the subject was asked to make a saccade to the location of the peripheral LED during the 'off' period. Presentation

TABLE 1. DETAILS OF PATIENTS

| Case     | Age<br>(yrs) | Sex | Field defect                       | Interval between onset<br>of lesion and testing<br>(yrs) | Aetiology                         |
|----------|--------------|-----|------------------------------------|----------------------------------------------------------|-----------------------------------|
| 1(L.A.)  | 38           | F   | R lower $\frac{1}{4}$ (incomplete) | 1                                                        | Haematoma                         |
| 2(C.B.)  | 27           | M   | L $\frac{1}{2}$                    | 3                                                        | Occipital AVM                     |
| 3(J.B.)  | 60           | M   | L $\frac{1}{2}$                    | 1                                                        | Infarction                        |
| 4(R.C.)  | 27           | M   | R upper $\frac{1}{4}$              | 4                                                        | Infarction<br>(migraine)          |
| 5(A.C.)  | 74           | M   | L $\frac{1}{2}$                    | 3                                                        | Infarction                        |
| 6(B.C.)  | 71           | F   | R $\frac{1}{2}$                    | $\frac{1}{2}$                                            | Infarction                        |
| 7(C.C.)  | 71           | M   | L $\frac{1}{2}$                    | 10                                                       | Infarction                        |
| 8(J.C.)  | 50           | M   | R $\frac{1}{2}$                    | $\frac{1}{4}$                                            | Infarction                        |
| 9(M.C.)  | 51           | M   | L $\frac{1}{2}$                    | 1 month                                                  | Infarction                        |
| 10(C.H.) | 60           | M   | R $\frac{1}{2}$                    | Unknown                                                  | Infarction                        |
| 11(J.H.) | 45           | F   | R $\frac{1}{2}$                    | 1                                                        | Infarction                        |
| 12(W.H.) | 59           | M   | R upper $\frac{1}{4}$              | $\frac{1}{2}$                                            | Infarction                        |
| 13(S.J.) | 42           | F   | L $\frac{1}{2}$                    | 19                                                       | Infarction                        |
| 14(A.L.) | 74           | M   | L $\frac{1}{2}$                    | $\frac{1}{2}$                                            | Infarction                        |
| 15(R.L.) | 20           | M   | Inferior altitudinal<br>defect     | 12                                                       | Trauma                            |
| 16(E.M.) | 64           | M   | L $\frac{1}{2}$                    | 1                                                        | Infarction                        |
| 17(B.P.) | 50           | F   | R $\frac{1}{2}$                    | Unknown                                                  | Infarction                        |
| 18(H.Q.) | 74           | M   | L $\frac{1}{2}$                    | 2                                                        | Infarction                        |
| 19(A.R.) | 55           | M   | R $\frac{1}{2}$                    | $\frac{1}{4}$                                            | Occipital lobec-<br>tomy (glioma) |
| 20(H.R.) | 54           | M   | R $\frac{1}{2}$                    | 1                                                        | Infarction                        |
| 21(M.R.) | 46           | M   | R $\frac{1}{2}$                    | $\frac{1}{2}$                                            | Infarction                        |
| 22(B.S.) | 63           | M   | R $\frac{1}{2}$                    | $\frac{1}{2}$                                            | Infarction                        |
| 23(H.W.) | 18           | F   | L $\frac{1}{2}$                    | 18                                                       | Infarction                        |
| 24(B.W.) | 51           | F   | R $\frac{1}{2}$                    | Unknown                                                  | Infarction                        |
| 25(G.Y.) | 27           | M   | R $\frac{1}{2}$                    | 12                                                       | Trauma                            |

$\frac{1}{4}$  = homonymous quadrantanopia;  $\frac{1}{2}$  = homonymous hemianopia. AVM = arteriovenous malformation. L = left; R = right.

of the peripheral LEDs was interspersed with blank trials in which no LED came on after the central fixation LED went 'off'.

#### Manual Localization

In this experiment, a modified Aimark perimeter was used with the subject's head supported by a chin and forehead rest, and the subject fixated monocularly a central cross when a peripherally located 1.7° spot (luminance 70 cd/m<sup>2</sup>) was presented for 100 ms. The subject was asked to point, with the forefinger of the hand ipsilateral to the target, to the position on the perimeter arc at which the spot appeared. This position, together with the actual position of the spot, was recorded on a visual field chart. Stimuli was randomly presented along the 45° meridians at either 20, 40, or 60° from the central fixation cross. The random sequence consisted of a total of 72 trials (6 trials for each position) split into 3 runs each of 24 trials with a 2 min rest between each run.



### *Pattern Discrimination*

The subject was seated in darkness in front of a white screen, in the middle of which was a bright LED which the subject was asked to fixate binocularly. Stimulus patterns, in the form of 35 × 35 mm black and white slides, were projected for 300 ms, under computer control, at a selected location in the visual field relative to fixation. Two pairs of patterns were used; one consisted of an equilateral triangle of side length 4°, and a circle of diameter 4°, the two being projected so that their images yielded the same total light flux. The other pair were a black and white square waveform grating of spatial frequency 1 cycle/deg and subtending 4°, one orientated horizontally and the other vertically. Initially, the subject viewed the stimuli in the normal hemifield and was then asked to state which of the pair of patterns was flashed on at each subsequent trial. Runs of 100 trials for each pair of stimuli were randomly presented so that half appeared in the normal field and half in the blind field.

Central fixation of the eyes was monitored using eye movement recordings obtained by d.c. oculography.

### *Movement Sensitivity*

Psychophysical measurements were made with stimulus patterns generated optically with a Maxwellian view system which provided up to four channels (Barbur and Ruddock, 1980; Holliday and Ruddock, 1983). The subject's eye position was maintained centrally relative to the 2 mm exit pupil by biting onto a dental clamp, and the effective pupil size of the steeply converging light beam at the eye was 0.6 mm. The instrument was designed to provide targets of chosen shape which can be moved horizontally across the field of view, at constant velocity in the range 0 to 100 deg/s, the direction of motion reversing on alternate presentations. The visual fields employed in each class of measurement are illustrated with the experimental data. A dim red fixation point enabled the stimuli to be presented at any selected position in the visual field, and illumination levels were calibrated with a Macam Instruments Radiometer.

### *Critical Fusion Frequency (CFF) for Flickering Lights*

This was measured with a circular target of diameter 5.5°, which was modulated sinusoidally in time by inclusion of fixed and rotating polaroids in the Maxwellian view system. A fixation point was provided and the target was located in the required area of the visual field relative to this point. The flicker frequency was increased slowly from a very low rate until a point was reached when the subject reported that the flickering had disappeared. CFF values were recorded as a function of the target illumination.

### *Anatomical Localization of the Retrogeniculate Lesions*

CT brain scans were obtained. These were performed in a plane approximately 15° to the horizontal plane or Reid's baseline. The extent of the lesions was determined by comparison with tracings taken from published CT scans with anatomical correlations (McAuley and Ross Russell, 1979; Gadow *et al.*, 1979).

### *Saccadic Training Programme*

Three subjects with complete homonymous hemianopias were given a portable LED display unit to take home. Each unit consisted of nine high intensity LEDs mounted along a collapsible metre rule. Each LED emitted yellow light with peak wavelength at 583 nm, was of luminance 320 cd/m<sup>2</sup> and subtended 0.5° at the eye. For a subject viewing distance of 50 cm, the separation between each LED was 15° and the total range was ±45°. The LEDs were electronically driven such that the central fixation LED was 'on' for 3 s followed by a 3 s presentation of another randomly selected peripheral LED, the sequence being continued cyclically. The subject was required to fixate the central LED and then search for the new target when the central LED was turned off. This necessitated saccades into both the blind and normal field. Subjects were instructed to use the equipment for

20 min every day for a period of one month, and to carry out the tests in a dimly lit room. We note that Zihl (1981) found that recovery following a similar training programme was less successful in reducing the field defects of hemianopes with a sharply defined visual field border than subjects with a more shallow gradient of light sensitivity between the intact visual field and the scotoma.

## RESULTS

Five of the 25 subjects with perimetrically determined homonymous field scotomas were able to detect certain types of light stimulus presented in the blind field, namely bright flashes and rapidly moving targets, and the visual fields measured for these subjects are shown in fig. 1. In each case, the subject was unable to identify any characteristic of the stimulus, being aware only of a transient (flashed or moving) shadow localized within the 'blind' field. These 5 patients were studied extensively using the experimental methods outlined above, and a further 11

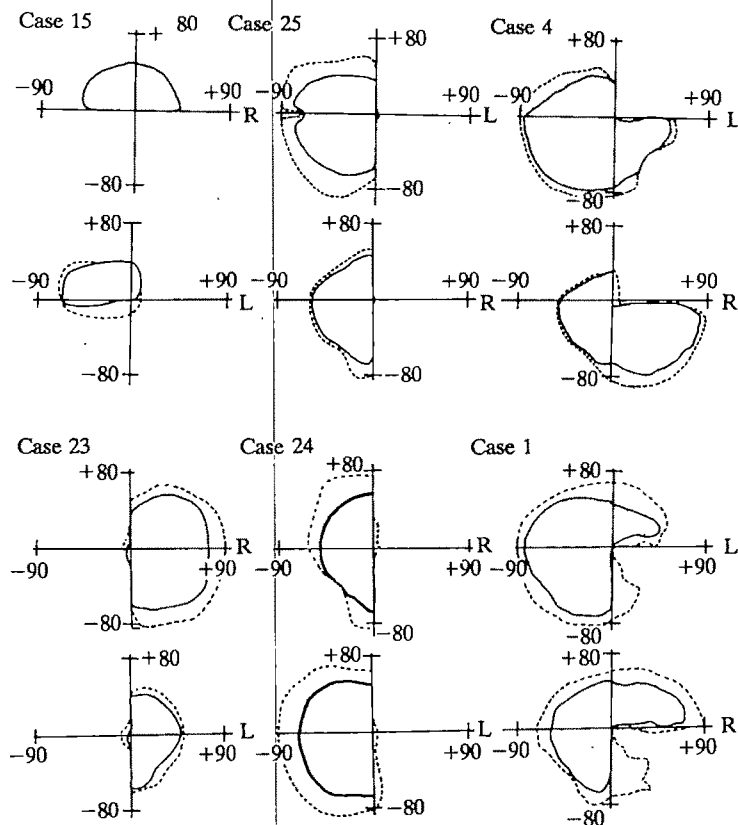


FIG. 1. Visual fields, measured with a Goldmann perimeter for each eye of 6 subjects, whose case numbers are given at the top left of each field plot. R and L to the right of the horizontal axis denotes the right and left eyes, respectively. Each plot shows the vertical and horizontal meridian plotted conventionally, +ve angles denoting upper hemifield and right hemifield for the respective axes. The detection limits for a large target ( $V = 64 \text{ mm}^2$ ) are shown by the broken line, and that for a small target ( $II = 1 \text{ mm}^2$ ) by a continuous line. The target was moved at  $2-3^\circ$  from the field periphery towards the centre and the limits denote positions of first detection. The targets were of luminance  $320 \text{ cd/m}^2$  and the background  $3.2 \text{ cd/m}^2$ .

patients were tested only in selected experiments (Table 2). The remaining 9 subjects who showed no residual vision to confrontation testing had their visual fields plotted, but were not available for further testing. These confrontation tests involved examination of detection and localization of bright flashes of light or of large fast-moving objects presented within the 'blind' field. Such tests differentiated accurately between the 5 subjects who were able subsequently to respond to the more controlled stimuli described in this paper, and those 9 who were not. We therefore classify 20 of our subjects as lacking residual vision, but cannot entirely exclude the possibility that under extensive examination some of the 9 subjects who revealed no ability to localize targets under confrontation may not have performed, statistically, above chance level in a manner characteristic of 'blindsight'.

Outline CT scans showing the extent of damage to the retrogeniculate pathways are shown in fig. 2.

TABLE 2. TESTS APPLIED TO 16 OF THE 25 SUBJECTS\*

| <i>Case</i> | <i>Saccadic<br/>localization</i> | <i>Manual<br/>localization</i> | <i>Pattern<br/>discrimination</i> | <i>Movement<br/>detection</i> | <i>Critical flicker<br/>fusion</i> |
|-------------|----------------------------------|--------------------------------|-----------------------------------|-------------------------------|------------------------------------|
| 1(L.A.)     | —                                | —                              | —                                 | +                             | —                                  |
| 2(C.B.)     | +                                | +                              | +                                 | +                             | —                                  |
| 4(R.C.)     | +                                | +                              | +                                 | +                             | +                                  |
| 7(C.C.)     | +                                | +                              | +                                 | —                             | —                                  |
| 8(J.C.)     | +                                | +                              | +                                 | —                             | —                                  |
| 9(M.C.)     | —                                | —                              | +                                 | —                             | —                                  |
| 11(J.H.)    | +                                | +                              | +                                 | —                             | —                                  |
| 12(W.H.)    | —                                | —                              | +                                 | —                             | —                                  |
| 13(S.J.)    | +                                | +                              | +                                 | —                             | —                                  |
| 14(A.L.)    | +                                | +                              | +                                 | +                             | —                                  |
| 15(R.L.)    | —                                | +                              | +                                 | +                             | +                                  |
| 17(B.P.)    | +                                | —                              | +                                 | —                             | —                                  |
| 19(A.R.)    | +                                | —                              | +                                 | —                             | —                                  |
| 23(H.W.)    | +                                | +                              | +                                 | +                             | +                                  |
| 24(B.W.)    | +                                | —                              | +                                 | +                             | +                                  |
| 25(G.Y.)    | +                                | +                              | +                                 | +                             | +                                  |

\* The other 9 subjects showed no ability to detect large moving or flashed objects, presented within their scotoma. + = test undertaken; — = test not performed.

### *Saccadic Localization*

Examples of the tests for saccadic localization are shown in fig. 3 for 7 hemianopic patients, and 1 normal subject (D.G.) who performs very accurate saccades to stimuli presented in either hemifield. A similar accurate saccadic localization is obtained for 2 patients, Cases 23 and 25, the former with a left and the latter with a right homonymous hemianopia (fig. 1). In all cases the increased SD at 0° represents saccades in the false trial when the subject searched for a target which did not appear. These 2 hemianopic subjects perceived the flashes as 'dark' shadows,

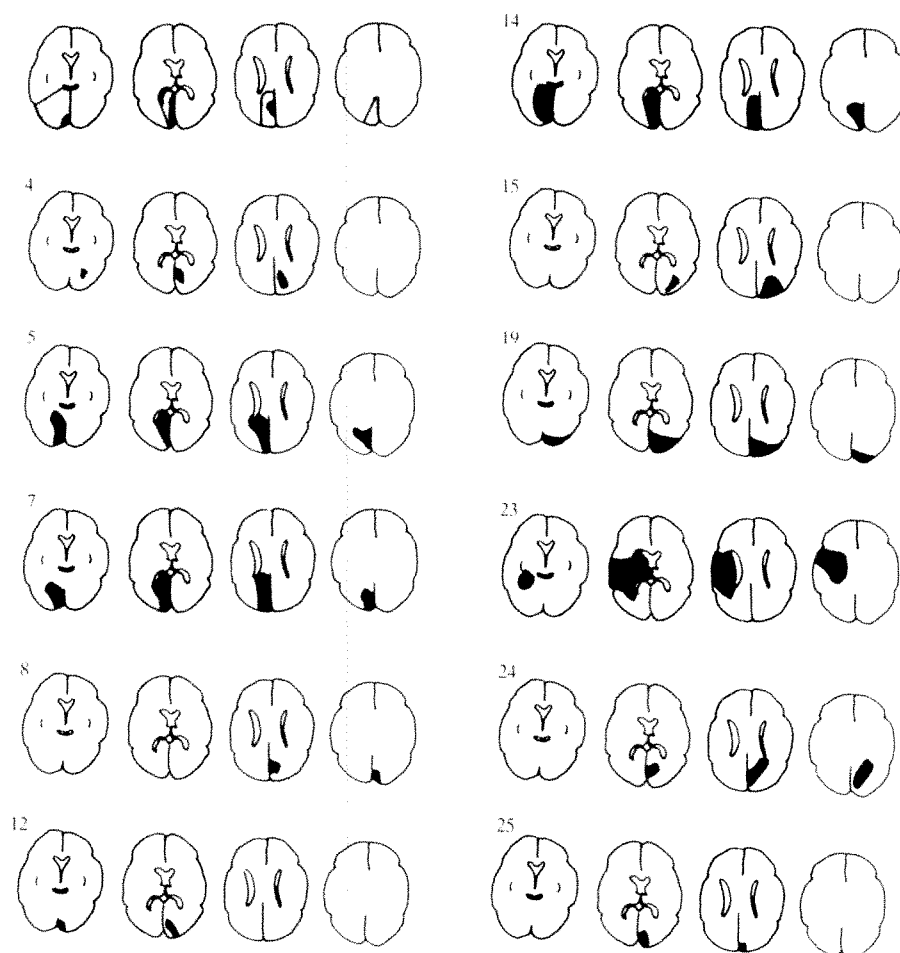


FIG. 2. Outline tracings of the CT brain scans from 11 subjects. Areas of low attenuation are shown in solid black. The templates are taken from McAuley and Ross Russell (1979). The upper left set of templates show the area of the calcarine cortex (black) and the territory supplied by the posterior cerebral artery (grey). The right side of the brain is shown on the left side of the template.

and in preliminary examination were identified as having residual vision. The other 5 hemianopic subjects made accurate eye movements only within their normal hemifields and saccades elicited by light flashes in the 'blind' hemifield did not, on average, deviate significantly from the zero (foveal) direction.

### *Saccadic Training Programme*

Three patients (Cases 2, 7, 14) with complete left homonymous hemianopic field defects, who had no conscious visual awareness of stimuli in their 'blind' field, and who failed to perform accurate eye movements to a target presented in the blind hemifield, were selected for this programme. The patients were all well motivated and had posterior cerebral infarctions which had occurred 6 months and 3 and 10 years, before testing. The visual fields were plotted and the saccadic localization

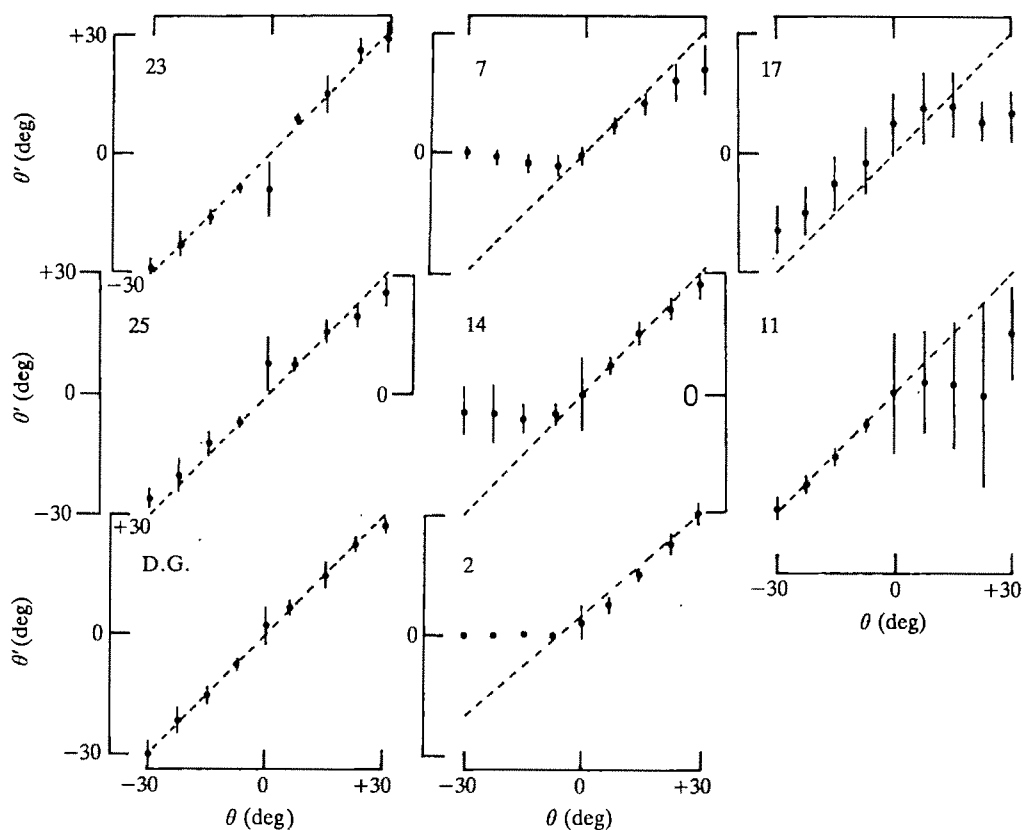


FIG. 3. The angle  $\theta'$  through which the eyes were moved in order to detect a light flash located on the horizontal meridian at angular location  $\theta$  from primary fixation (+ve angles denote the right hemifield). The lights were of diameter 23 min, wavelength 565 nm, duration 100 ms and luminance 56.2 cd/m<sup>2</sup>. Subject D.G. had normal vision, all other subjects were hemianopic; the cases numbers are given in the upper left corners of the panels. Error bars define the SEM for 10 readings.

test was performed both before the training programme and again within one week of its cessation. No change in their visual fields was noted after one month of saccadic training. The effect of the training programme on saccadic localization is shown in fig. 4. Comparison between two sets of measurements for Cases 2 and 7 reveals a much greater SD for the post training responses with little change in the mean locations.

### Manual Localization

Accurate localization of light flashes in the 'blind' field was found only in the same 5 patients who exhibited intact saccadic localization, and not in any of the remaining patients who were tested. Manual localization by these subjects showed a tendency to undershoot the target location.

The remaining results were obtained by measurement of thresholds for detection of transient stimuli and with one exception, refer to the 5 subjects capable of responding to stimulation of the 'blind' visual field.

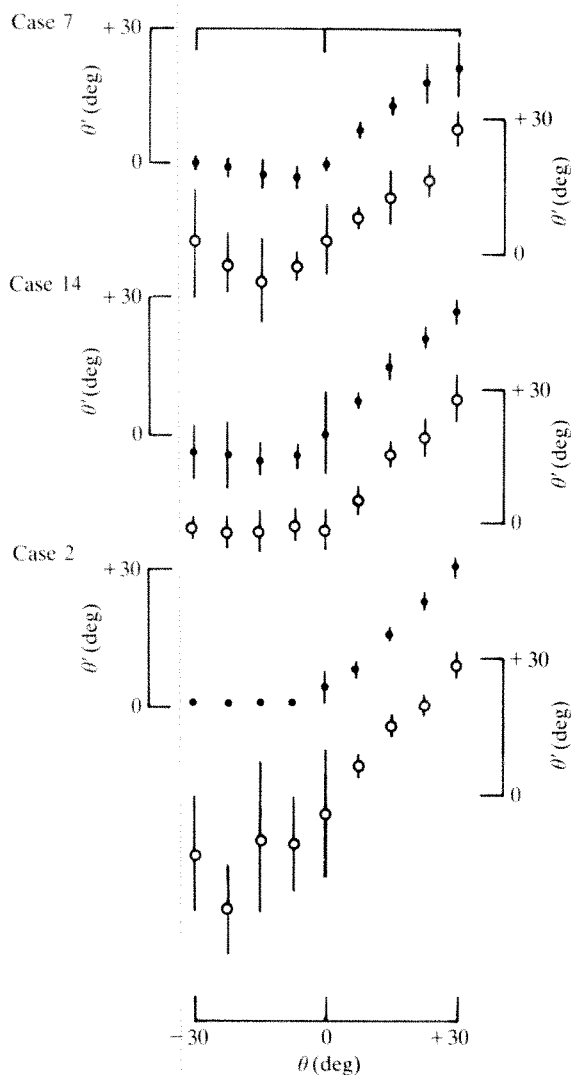


FIG. 4. Conditions as fig. 3 but two sets of data are given for each subject. Full circles correspond to values obtained before commencement of training, and are defined by the left hand  $\theta'$  scales. Open circles denote values obtained after 1 month's training and are defined by the right hand  $\theta'$  scale. Error bars again denote SEM for 10 readings.

### *Movement Detection*

Threshold illumination required for detection of a (circular) target moving with constant velocity,  $V$ , is plotted as a function of  $V$  in fig. 5. Values are given for both hemifields of the 5 subjects with residual vision in the 'blind' fields, and for Case 1, a subject with a large scotoma, but unable to detect transients presented within the scotoma, on confrontation. Comparison data are also given for a normal subject, I.B. The first 5 subjects all require high illumination for detection of low velocity targets presented in the blind hemifield, the value falling as the velocity

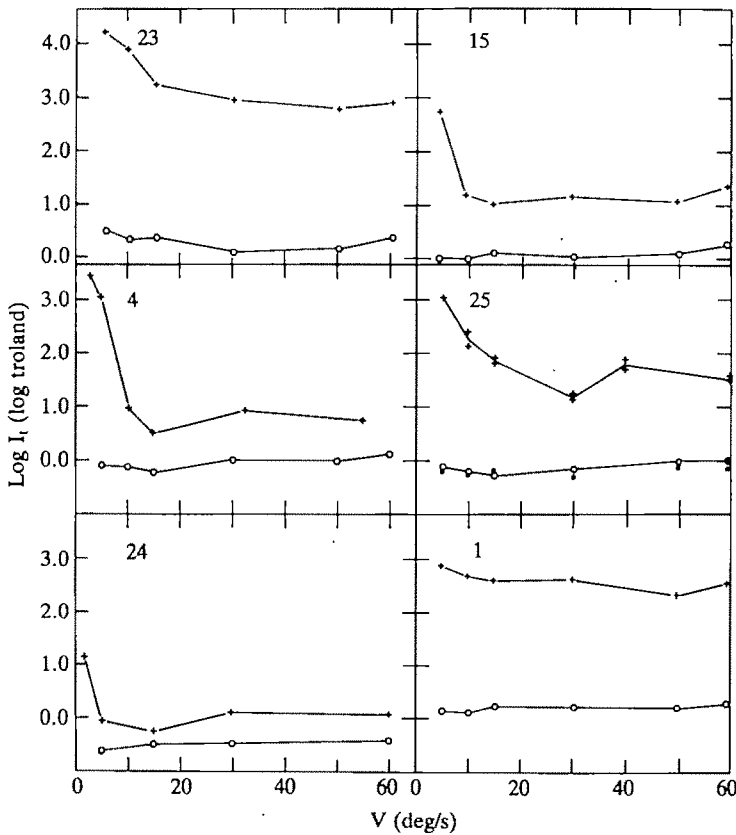


FIG. 5. Threshold illumination,  $\log I_t$ , for detection of a circular target (diameter  $3.5^\circ$ ) moving at  $V$  deg/s along a direction parallel to the horizontal meridian, against a uniform background of illumination 1 log troland. Case numbers are given in the top left of each panel. The target traversed  $8^\circ$ , and was located within the field scotoma (crosses) or in the corresponding position in the normal field (open circles). The target locations for each subject were: Cases 23–25,  $\pm 30^\circ$  along the horizontal meridian; Case 15,  $\pm 30^\circ$  along the vertical meridian; Case 4,  $\pm 30^\circ$  along the horizontal and vertical meridians; Case 1,  $\pm 15^\circ$  along the horizontal meridian,  $-30^\circ$  along the vertical meridian. Values of  $\log I_t$  are the means of 4 readings and the spread in these values was typically  $\pm 0.03$  log units. Full circles on the data plot for Case 25 denote comparison values for normal subject I.B.

increases, but have normal thresholds, similar to those for I.B., for detection in the 'normal' hemifield. In contrast, Case 1 requires approximately the same high illumination for all target velocities presented within the scotoma.

The directional selectivity of movement detection in the 'blind' hemifield was examined in detail for Case 25. The apparent direction of movement (left to right or vice versa) was determined for a circular spot moving at constant velocity along the horizontal meridian, the direction of successive presentations being randomized. Targets were presented at a series of contrast levels (both positive and negative) bridging threshold for detection of the target, and both contrast level and direction of movement were varied randomly between presentations. The subject responded to the target as seen or not seen, and in the former case identified the direction of movement as left to right or vice versa after each presentation. The probability,  $P$ ,

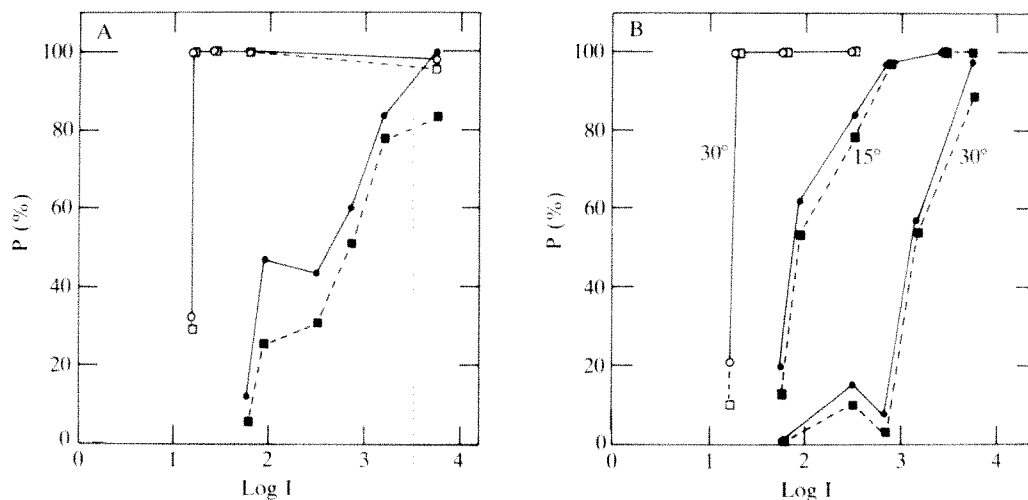


FIG. 6. Probability for detection of a circular target (diameter 3.5 deg), moving at 30 deg/s, through 8 deg displacement, against a background of illumination 1.2 log troland by Case 25. The target was located off-axis along the horizontal meridian, and the value of  $\log I$  denotes the target illumination for a bright spot (positive contrast), or that of the surround for a dark spot (negative contrast). A, data for a negative contrast target. Circles denote probability of target detection and squares the probability of correctly identifying the direction of movement. Open symbols refer to the normal and full symbols to the 'blind' hemifield. The target was located  $\pm 30^\circ$  off axis and probabilities refer to 50 observations at each point. B, data for a positive contrast target. Circles denote probability of target detection and squares the probability of correctly identifying the direction of movement. Open lines refer to the normal and full circles to the 'blind' hemifield, and the location of the target along the horizontal meridian is given, in deg, on the diagram. Probabilities refer to 50 observations at each point.

of correctly identifying the direction of target movement rises monotonically as target contrast increases, but the change with contrast is much more gradual for Case 25 than for the normal hemifield (fig. 6). There is, however, no evidence of ambiguity in the perceived direction of movement. Discrimination of movement direction for suprathreshold targets was examined by direct comparison between two successive presentations. The first was a reference target which moved parallel to the horizontal meridian and was always directed from left to right, whereas the second was the target and moved at angle  $\theta$  relative to the reference. Values of  $\theta$  were set at one of the four values:  $0^\circ$  (same),  $90^\circ$  (downwards),  $180^\circ$  (opposite), or  $270^\circ$  (upwards) (inset fig. 7), and the subject was asked to define the direction of the variable target, which was presented 2 s after the reference target. The probability of Case 25 correctly identifying the direction  $\theta$  is plotted on a polar diagram (fig. 7), and whereas values are high for  $\theta$  equal  $180^\circ$ , they are low for all other angles, and in particular, he made frequent errors for  $\theta=0$ , which he identified as 'upwards' or 'downwards' on about 80% of presentations. He never identified movement with  $\theta=180^\circ$  as being in the same direction as the reference, and only on 2 of 16 occasions did he identify  $\theta=0$  as being in the 'opposite direction' to the reference.

### Critical Fusion Frequency

Sensitivity for transient nonmoving stimuli was measured in terms of critical



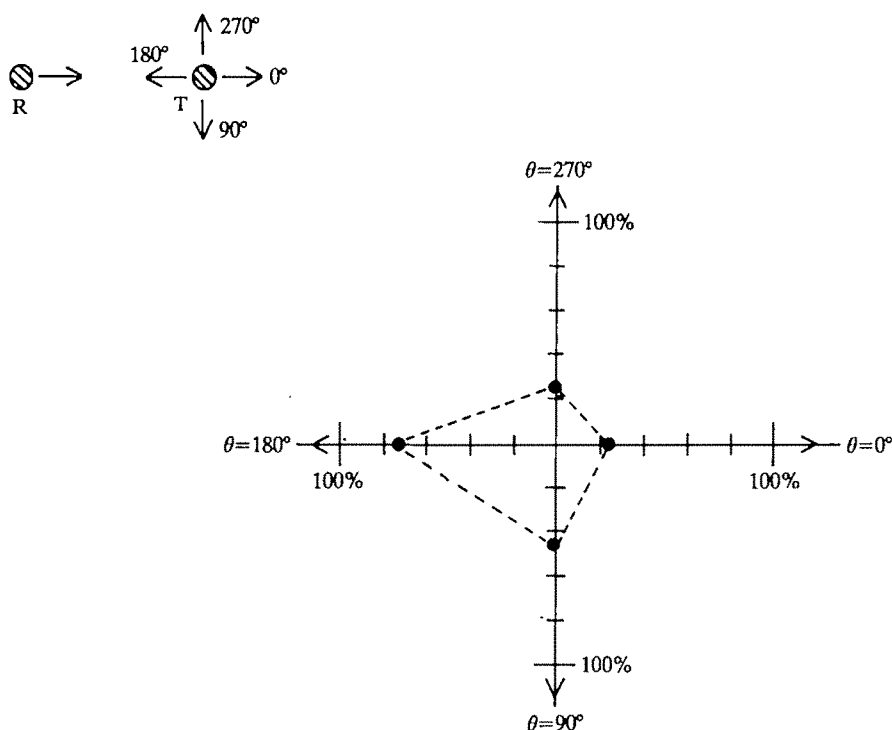


FIG. 7. The probability of correctly identifying the direction of movement of a target (T) relative to that of a reference (R) which moved along the horizontal meridian (see inset) by Case 25. The stimuli moved at 15 deg/s and were of 3° diameter and 3 log troland illumination. The stimulation were located 30° off-axis along the horizontal meridian and traversed 10 deg against a dark background. Probability values are given for each of the four directions of target movement and are based on 16 observations for each of the four values of  $\theta$ .

fusion frequency (CFF) at different illumination levels. Values for both normal and 'blind' visual field areas of all 5 subjects with residual vision are given in fig. 8, and in each case, those for the 'blind' areas are significantly lower than those for the normal fields.

### Pattern discrimination

Pattern discrimination was examined both for differentiation of target shapes and for the resolution of square waveform, one-dimensional, gratings. We found no evidence of discrimination with either task, by any of the 5 subjects, in response to targets located anywhere within the 'blind' areas of their visual fields. Thus they were unable to discriminate between the horizontally and vertically orientated gratings (1 cycle/deg) when they were presented, in random sequence, in 300 ms flashes. Similarly, the equilateral triangle and the circle were indistinguishable from each other at any location in the 'blind' hemifield as has already been reported for presentation 30 deg off-axis in 'blind' hemifield for Case 25 (Barbur *et al.*, 1980).

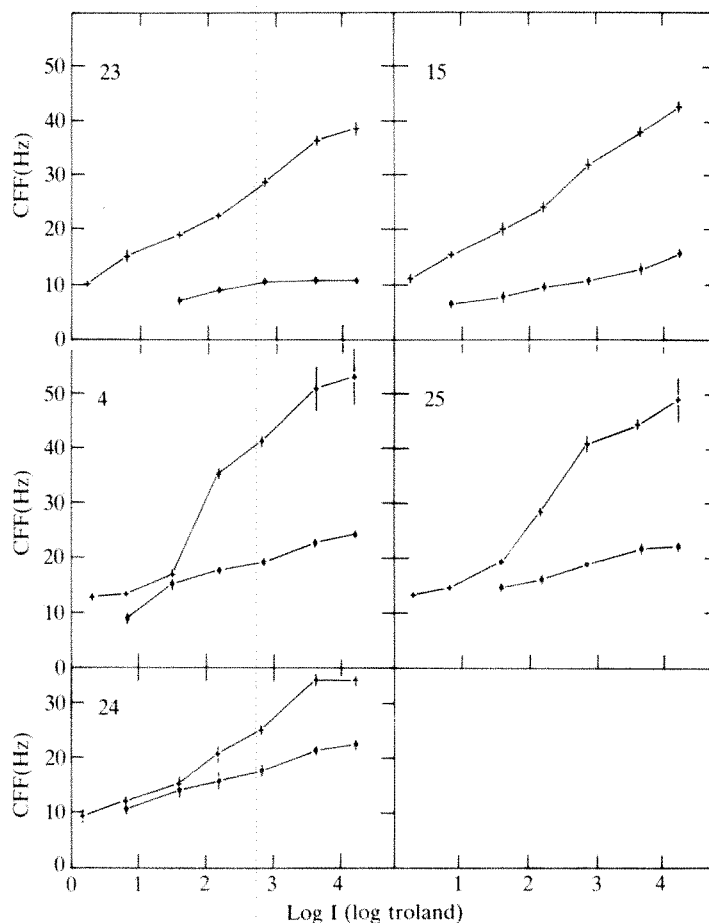


FIG. 8. Values of critical fusion frequency (CFF) (Hz) plotted against the logarithm of the target illumination (log I). The case numbers are given at the top left of each panel. The sinusoidally modulated target (diameter 5.5°) was superimposed on a uniform background of illumination 0.75 log troland. Crosses refer to values for stimuli located within the scotoma and full circles to values for the corresponding location in the normal hemifield. Stimulus locations for each subject are the same as for fig. 5.

### Colour discrimination

The possibility of colour discrimination using the 'blind' retinal areas was investigated by presentation of monochromatic lights (300 ms flashes) within these areas and asking the subject to name the stimulus colour. Only 1 subject (Case 24) reported any sensation of colour and she consistently identified 635 nm, and 530 nm flashes as red and green, respectively.

### DISCUSSION

Our survey of 25 subjects with visual field losses associated with damage of the striate cortex shows that 5 of them are capable of restricted responses to visual

stimuli presented within the 'blind' field. These 5 all experience a sensation of a dark shadow, localized within their 'blind' fields, when stimulated by transient changes in illumination of either positive or negative contrast. They can perform accurate eye movements in response to light flashes located in the 'blind' field (fig. 3), and the ability to perform such eye movements provides a reliable indication of whether a given subject possesses residual vision. None of the remaining 20 subjects showed any capacity for visual localization or pattern discrimination in the screening experiments (*see Results*).

Sensitivity to detection of moving targets increases with displacement velocity, although the peak sensitivity achieved varies considerably between the 5 subjects. For example, Case 23 remains relatively insensitive for a target velocity of 60 deg/s (about 2.6 log units less sensitive than in the normal fields), whereas Cases 4 and 24 have sensitivity approaching that of their normal fields for target velocities above about 15 deg/s. The properties of this movement detection mechanism were studied in detail only in Case 25. At near-threshold contrast, he differentiated correctly between movement directed in opposite directions (fig. 6), whereas his discrimination of movement in orthogonal directions is relatively poor (fig. 7). This movement detection mechanism for residual vision in his 'blind' hemifield is, therefore, characterized by low directional selectivity, but it has been shown previously that it is capable of normal speed discrimination (Barbur *et al.*, 1980, fig. 11). Critical fusion frequency (CFF) saturates at abnormally low values for 'blind' field responses in all 5 subjects (fig. 8); thus although residual vision is transient in nature, it is characterized by a low frequency temporal response. It has been shown that for Case 25, spectral sensitivity in the 'blind' field at locations, such as those used in the determination of CFF, is scotopic (Barbur *et al.*, 1980). Rod vision is characterized by low frequency CFF (Hecht and Schlaer, 1936) and thus it could be argued that the low CFF values reflect the dominant rod contribution to residual visual responses. For Cases 15 and 23, however, CFFs rise to a value significantly below the peak of 16–18 Hz found for rods, even though the illumination levels employed were well above that required to saturate rod vision (Aguilar and Stiles, 1954). We consider it more likely that the low CFF values reflect the largest increment threshold required for detection of the test flashes in the 'blind' hemifield, and there is a weak correlation between the CFF data and sensitivity in detection of moving targets. Case 23, for example, suffers the greatest loss for both functions. Greater numbers of subjects are required in order to examine systematically this correlation.

It has been shown recently that for 2 of these subjects, discrimination of displacement between two light stimuli switched on briefly in sequence demonstrates near normal spatial resolution when this task is performed within the 'blind' field (Blythe *et al.*, 1986). Both subjects require larger displacements of the two spots to achieve the same performance level as an experienced normal subject, but were able to discriminate transient displacements at spot separations at which the two spots were indistinguishable from a single spot. The lack of pattern recognition

and discrimination within the 'blind' field establishes a striking dissociation between those tasks and the discrimination of transient displacement. The visual mechanisms serving the 'blind' field areas, and which mediate residual vision, appear to lack the capacity for construction of spatial patterns. This was confirmed by presenting Case 25 with sequentially flashed spots, arranged to form a geometric pattern such as a triangle (· · ·). Although in this case he was aware that the three spots were not colinear, he was unable to identify the geometric shape formed by them. The near normal ability to locate objects in the 'blind' field cannot, therefore, be exploited in the recognition of spatial patterns.

Three possible mechanisms for residual vision have been considered. First, some authors have suggested that one possible cause of residual vision is activity in the remaining neurons surviving in the striate cortex sustaining only partial destruction (Pöppel *et al.*, 1973; Campion *et al.*, 1983), although obviously this cannot apply to cases in which there has been surgical ablation of the whole hemisphere (Perenin and Jeannerod, 1978). Such an explanation requires that a group of neurons capable of the localization and detection of transients without providing pattern recognition or sustained responses, remains active in the striate cortex. Although this cannot be excluded, it implies a degree of parallel organization at striate level which has proved difficult to establish, even by those committed to such a view of cortical organization (*see e.g.*, Stone, 1983).

Secondly, the recently described projection from the lateral geniculate nucleus to the prestriate cortex (Benevento and Yoshida, 1981; Fries, 1981; Yukie and Iwai, 1981; Bullier and Kennedy, 1983) could also contribute to residual visual function in subjects suffering damage of the striate cortex, and may, for example, provide a neural base for the unexpected colour discrimination found for Case 24.

Thirdly, there is the most probable candidate, the retinocollicular pathway which projects to the extrastriate visual cortex via the pulvinar. The transient nature of the visual responses studied by us is consistent with the responses recorded electrophysiologically from neurons in the superficial layers of the superior colliculus, as described in the Introduction, and the comparison between the two kinds of responses was described in detail by Barbur *et al.* (1980).

The ability of subjects to resolve, normally, target displacement in the 'blind' field, without any pattern recognition or pattern discrimination capacity, is consistent with the activity of a visual pathway concerned with 'where' rather than 'what', as proposed in the two systems interpretation of visual organization (Schneider, 1969).

There is no obvious correlation between the degree of cortical damage revealed by CT brain scans (fig. 2) and the incidence of residual vision. Lesions damaging the striate cortex alone, or involving, in addition, surrounding prestriate cortex and underlying white matter were found in patients of both groups. Examination of the medical records of our subjects suggests that the age at which brain damage occurs may be a significant factor in determining whether or not they exhibit residual vision. Three of the 5 subjects with residual vision suffered a lesion to their

visual pathways when aged 11 yrs or younger (Cases 15, 23, 25), the fourth (Case 4) when aged 23 yrs; the fifth (Case 24) is unsure of the onset of visual field loss or of any medical incident which could have caused such loss, and thus it may have been present from an early age. In only 1 of the other 20 subjects does the history of visual disturbance predate the age of 20 yrs. Five of the 6 subjects with residual vision studied by Perenin and Jeannerod (1978) were aged less than 10 yrs when they received their hemidecortication, but other reports have shown evidence of residual vision in subjects in whom the lesion occurred at a considerably later age (Weiskrantz *et al.*, 1974; Zihl and von Cramon, 1979; Ross Russell and Bharucha, 1984). It will be of interest to examine the significance of the age at which visual loss occurs in a larger population of subjects.

Finally, the value of training techniques in reducing the size of the scotoma is controversial (Bailliet *et al.*, 1985; Zihl and von Cramon, 1985). Although we found no such reduction in our 3 subjects who performed saccadic training for one month, we did find in 2 of them an increased number of larger saccades toward the blind hemifield, which may be of functional importance. Unfortunately there are no data concerning any possible alteration in saccadic strategy following saccadic training in a large series of patients who underwent such training (Zihl and von Cramon, 1985). It has been shown for a single patient, following an occipital lobe lesion, that changes in eye movement strategy may occur naturally with time (Meienberg *et al.*, 1981). The possible contribution of other sensory modalities to the recovery of partial visual function following cortical damage (De Vos-Korthals and Van Hoff, 1985) also seems worthy of experimental study in human subjects.

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## A STUDY OF VIRAL GENOMES AND ANTIGENS IN BRAINS OF PATIENTS WITH ALZHEIMER'S DISEASE

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### SUMMARY

The presence of viral nucleic acid sequences and antigens from a variety of conventional viruses in selected brain regions of cases of Alzheimer's disease (AD), diagnosed pathologically, was investigated using molecular hybridization and immunocytochemical techniques. Seven DNA and 4 RNA viruses were used as probes in 18 AD and 5 control brains. With Southern blot hybridization, no viral DNA sequences could be detected in the cerebral cortex. With dot blot hybridization, results were also negative, except for 2 cases, 1 a control brain, the other an AD brain, which gave a positive signal in the RNA extracted from the substantia innominata when c-DNA from measles virus was used as a probe. Four specific brain areas from each of 8 AD brains and 5 controls tested with viral probes (3 DNA and 5 RNA viruses), using immunocytochemical techniques for viral antigens, showed no positive reproducible specific reactions. These results, although negative, do not totally exclude the possibility that conventional viruses may play a role in the aetiology and pathogenesis of AD.

### INTRODUCTION

The specific aetiology and pathogenesis of Alzheimer's disease (AD) remain unknown. The main thrust of work in the last 5 to 10 years has been on the neurochemical and neuropathological correlates of this primarily dementing illness. As in other degenerative disorders of the nervous system of unknown origin, viral and immunological causes have been suggested but there is, in fact, a paucity of actual data available on these otherwise testable hypotheses. Three lines of evidence have suggested the possibility of a replicating agent in AD and senile dementia of Alzheimer type (SDAT). The clinical transmission of 2 cases of familial AD to 3 chimpanzees was reported, but this was expressed histologically as Creutzfeldt-Jakob disease (CJD) a spongiform encephalopathy, rather than as the specific lesion of AD (Rewcastle *et al.*, 1978). Subsequent updating of this NIH study (Goudsmit *et al.*, 1980) showed no further positive transmission, even with the affected primates having had survival times characteristic of CJD. No encephala-



lopathy with the classic AD pathology has been transferred to animals to date (1986). An intriguing paper from Canada reported the production of paired helical filaments of the AD type in human fetal cerebral cortex neurons cultured in AD brain material (De Boni and Crapper, 1978); these induced changes, however, have not so far been repeated. A third line of evidence suggestive of a replicating agent in AD involves the scrapie agent, which, when inoculated into the CNS of certain recipient mouse strains, induced the formation of neuritic plaques similar to those of AD (Bruce and Fraser, 1975). This was the first recognition of an association between neuritic plaques and an infectious agent. Data from Prusiner's laboratory have suggested that a protease-resistant protein is a structural component of the infectious scrapie prion (McKinley *et al.*, 1983), and that the latter can aggregate to form amyloid-like birefringent rods (Prusiner *et al.*, 1983), raising the possibility that the amyloid plaques observed in AD and in the human transmissible encephalopathies (i.e., kuru, CJD, Gerstmann-Straussler syndrome), might be composed of prions. Marsh *et al.* (1984) have reported data consistent with the conclusion that the scrapie agent is a complex of macromolecules rather than a free infectious protein, lipid, nucleic acid or nucleoprotein. Rohwer (1984) has reported that the sensitivity of the scrapie agent to heat inactivation differs only in degree from that shown by conventional viruses; in carefully controlled kinetic experiments, scrapie infectivity was found to be sensitive to temperatures of 100° C or greater in a manner consistent with the behaviour of conventional viruses. This interesting set of data on the scrapie agent is not inconsistent with the structure of conventional viruses. Most recently, Gajdusek's group (Brown *et al.*, 1986), using Western blot tests on purified fractions of brain tissue from cases of spongiform encephalopathies and controls (the latter including 14 AD brains) against an antiserum to similarly purified fractions from scrapie-infected hamster brain, showed 'results that do *not* support the hypothesis that Alzheimer's results from infection with an agent similar to the agent that causes Creutzfeldt-Jakob disease', consistent with their own previous unsuccessful attempts to transmit the disease.

The role of conventional viruses in AD, which may be involved in an unusual manner, has not been carefully investigated to date, despite the fact that such viruses have been implicated in subacute sclerosing panencephalitis (measles) (Payne *et al.*, 1969), progressive multifocal leukoencephalopathy (papovavirus-JC) (Walker, 1978) and progressive rubella panencephalitis (Coyle and Wolinsky, 1981). It is worth noting that none of these conventional viruses transmitted in the manner of scrapie, kuru and CJD. A report on the limited serological survey of 14 AD patients showed no unusual antibody levels to a range of classical viruses (Whalley *et al.*, 1980). A report that herpes simplex virus (HSV) genome was detected in 2 brains with senile plaques and neurofibrillary tangles (Sequiera *et al.*, 1979) could not be confirmed by another study on 3 AD brains (Middleton *et al.*, 1980). A positive immunoperoxidase reaction of HSV surface antigens was reported in a case of AD which came to biopsy, using the unlabelled antibody-enzyme (PAP) method (Mann *et al.*, 1981). Using a spot dot hybridization technique, Taylor *et al.* (1984) were

unable to demonstrate HSV sequences in human brains from 8 cases of dementia of the Alzheimer type and 9 nonneurological control patients.

In this study, we have looked for the presence of viral nucleic acid sequences and antigens from a variety of conventional viruses in selected brain regions of histologically confirmed cases of AD. Our working hypothesis is that the basic brain lesions of AD, neurofibrillary tangles and neuritic plaques, could be the late result of a host reaction to a previous viral infection or the product of a masked viral genome which does not replicate but becomes integrated into the host DNA or persists as an independent element. Considering the high frequency of AD, it can be further postulated that ubiquitous conventional viruses that infect large portions of the population (rather than rare unconventional agents) may be involved at some stage in the development of brain lesions.

## MATERIALS AND METHODS

### *Brain DNA and RNA Hybridizations*

Samples obtained from selected brain regions (cerebral cortex, substantia innominata) from 18 cases of previously histologically diagnosed AD and from 5 age-matched controls diagnosed as normal brains were stored at  $-70^{\circ}\text{C}$ . In all 18 cases of AD and 5 controls, cerebral cortex was available for this portion of the study, but substantia innominata was available only in 6 cases of AD and 2 controls. Approximately 1 to 2 cm<sup>3</sup> in size were washed with cold phosphate-buffered saline, minced in TES (Tris-HCl buffer 0.1 M pH 7.8, EDTA 1 mM and NaCl 0.15 M) and homogenized. The homogenate was brought up to 0.5% 'Sarkosyl' and incubated with 1 mg/ml of proteinase K at  $37^{\circ}\text{C}$  overnight. Nucleic acids were extracted with TES-saturated phenol, precipitated with 2 volumes of ethanol and centrifuged at 1,000 g for 30 min in a Sorval refrigerated centrifuge. The precipitates were resuspended in 0.1 M Tris-HCL buffer pH 7.8 with 10 mM EDTA and incubated with either 50 U/ml of ribonuclease A or 1,000 U/ml of DNase I for 2 h at  $37^{\circ}\text{C}$ . The remaining DNA or RNA was extracted with phenol and precipitated with alcohol as described above. The amount of DNA or RNA recovered was measured by the Burton's reaction (Burton, 1956), or by absorption at 260 nm in a Gilson spectrophotometer.

DNA from the following viruses was used in these experiments: *vaccinia* virus (prepared in our laboratory (Pogo *et al.*, 1977); *herpes simplex* virus I and II and cloned *hepatitis B* virus DNAs (obtained from Dr Nigel Fraser and Dr Charles Tuckney); *cytomegalovirus* (CMV) DNA (a gift of Dr Edward Lee); *adenovirus 2* and *SV<sub>40</sub>* DNAs obtained from commercially available sources (Sigma). Cloned c-DNA from *poliovirus*, cloned DNA from the nucleoprotein gene of *influenza virus A* and from the haemagglutinin gene of *influenza virus B*, and cloned DNA from the nucleocapsid gene of *measles* virus were obtained from Drs Eckard Wimmer, Peter Palese, and William Bellini, respectively.

For detection of RNA virus sequences, two different hybridization techniques were used: Southern blot of restricted DNA (Southern, 1975) and dot blot of total brain RNA (Lin, 1985). In both cases, the probe was the cloned c-DNA of RNA viruses.

The viral DNAs were nick-translated using <sup>32</sup>S-nucleotides (New England Nuclear) and the enzymes purchased from BRL following the conditions described by Rigby *et al.* (1977). The average specific activity of these viral probes was around 10<sup>8</sup> cpm/μg of DNA. Brain DNA and an aliquot of the viral DNA to be probed were digested with EcoRI (from BRL) according to the conditions recommended by the manufacturer. The restriction fragments were separated by electrophoresis in 0.6% agarose gels and then transferred to nitrocellulose filters (Southern, 1975). Hybridizations were performed under stringent conditions according to the technique described by Maniatis *et al.* (1982). After carefully washing the filters, the radioactivity was monitored by autoradiography with x-ray films.

All the hybridizations were performed in duplicate. Dot blot hybridization using brain RNA was carried out following the conditions described by Lin *et al.* (1985).

#### *Immunocytochemical Detection of Viral Antigens*

Sections from the frontal lobe (Brodmann 10), temporal lobe (Brodmann 21/22), hippocampus and substantia innominata (nucleus basalis of Meynert) of 8 pathologically confirmed cases of AD and 5 age-matched normal control brains were studied for viral antigens, using the following techniques: (1) immunofluorescence, mainly avidin FITC-biotinylated antibody procedure (Heggeness and Ash, 1977) and rarely, the indirect immunofluorescence technique, with cryostat sections; (2) peroxidase-antiperoxidase complex (PAP) technique (Sternberger, 1978) and, occasionally, the avidin-biotin-peroxidase complex (ABC) method (Hsu *et al.*, 1981), with paraffin-embedded sections.

Formalin-fixed paraffin-embedded sections only were available from 4 AD cases, freshly cryostat-cut sections only from 2 AD cases, and both types of sections from the remaining 2 AD cases. All sections were 6  $\mu$ m thick; sections adjacent to those used for immunocytochemical tests were checked for the presence of senile plaques with thioflavin-S (Schwartz *et al.*, 1964) and found positive in all instances. Similar brain sections from controls were used.

The following immune sera were used as probes: *cytomegalovirus*, *herpes simplex virus type 1*, *vaccinia*, *influenza A*, *measles*, *mumps*, *respiratory syncytial virus*, and *rubella*. All sera were obtained from commercial sources, except for *vaccinia* which was prepared in our laboratories. The sera derived from goat, guinea pig or rabbit and each immune serum had, as corresponding control, a preimmune sample taken from the same animal. The sera had been tested by the supplier by complement fixation, neutralization or haemagglutination-inhibition tests and had high titres.

## RESULTS

#### *Molecular Hybridization*

Experiments with known amounts of viral DNA added to a fixed amount of brain DNA indicated that it was possible to detect as little as 0.1 ng of viral DNA in the presence of 50  $\mu$ g brain DNA ( $10^7$  cells). The results of representative experiments are shown in figs 1 and 2. In fig. 1, different amounts of c-DNA from measles (lanes 1–6) mixed with brain DNA or alone were digested with EcoRI, electrophoresed, blotted unto nitrocellulose paper and hybridized with labelled measles virus c-DNA. The probe was able to recognize 0.1 ng of measles DNA (lane 5) in the presence of brain DNA. The same amount of c-DNA without brain DNA gave a signal of almost similar intensity (lane 8). Likewise, when CMV DNA was employed, it was found that the probe was able to detect 0.1 ng of viral DNA (fig. 2, lane 3) in the presence of 50  $\mu$ g of brain DNA. It should be emphasized that the molecular weight of the viral DNA used in these experiments varied from  $2 \times 10^6$  daltons (hepatitis B) to  $160 \times 10^6$  daltons (cytomegalovirus), so the limit of sensitivity of the procedure is about 1 genome equivalent per cell for a viral DNA of a MW of  $10^8$  daltons such as herpes virus DNA.

The results obtained with Southern blot hybridization, as summarized in the Table, indicated that no viral DNA sequences could be detected when the DNAs or c-DNAs obtained from the viruses mentioned in the Table were used as probes. Under the same experimental conditions, however, 0.1 ng of the viral DNA tested gave a positive signal. Furthermore, no specious hybridization between herpes

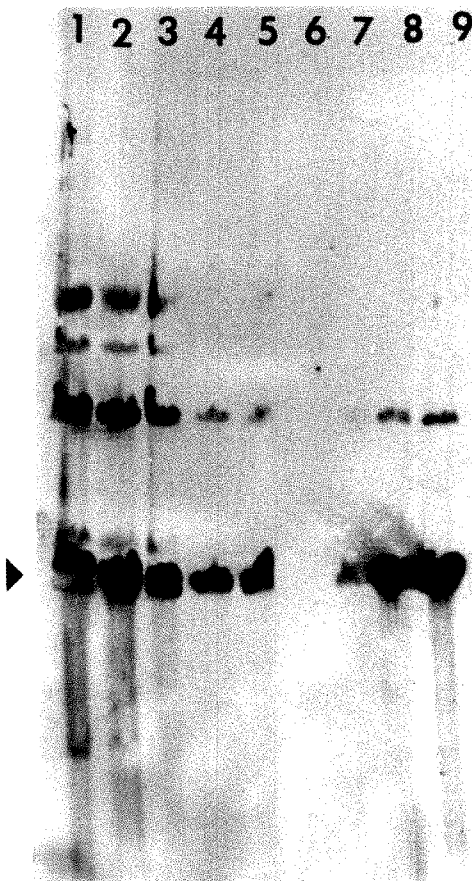


FIG. 1. Southern blot hybridization of brain DNA probed with measles c-DNA. Aliquots containing 50  $\mu$ g of brain DNA from a control case were mixed with 0.5  $\mu$ g (lane 1), 0.1  $\mu$ g (lane 2), 10 ng (lane 3), 1 ng (lane 4), 0.1 ng (lane 5) and 10 pg (lane 6) of measles c-DNA and digested with EcoRI. Lanes 7, 8 and 9 contain 0.01 ng, 0.1 ng and 1 ng of digested measles DNA alone, respectively. Conditions for electrophoresis, blotting and hybridization in Materials and Methods. The arrow indicates the position of the nucleocapsid gene.

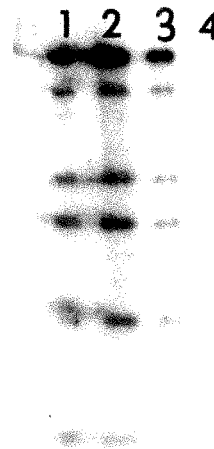


FIG. 2. Southern blot hybridization of brain DNA probed with CMV DNA. Aliquots containing 50  $\mu$ g of brain DNA from a control case were mixed with 1 ng (lane 1), 5 ng (lane 2), 0.1 ng (lane 3) and 0.01 ng (lane 4) of CMV DNA and digested with EcoRI. Conditions for electrophoresis, blotting and hybridization are described in Materials and Methods.

virus DNA and human DNA, as has been reported (Jones and Hyman, 1983), was observed, suggesting that the conditions of hybridization used here did not favour nonspecific nucleotide interactions.

The results of the hybridizations performed with RNA from cerebral cortex and substantia innominata by dot blot using cloned c-DNA from RNA viruses were also negative in most cases studied. However, in 2 cases out of 6 AD and 2 control cases, a positive signal was detected in the RNA extracted from substantia

TABLE. RESULTS WITH BRAIN DNA AND RNA HYBRIDIZATIONS

| <i>Virus tested</i> | <i>No. of cases</i>                       | <i>Areas studied</i>                        | <i>Procedure</i>                               | <i>Results</i>                                                                         |
|---------------------|-------------------------------------------|---------------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------|
| Cytomegalovirus     | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern                                       | All negative                                                                           |
| Vaccinia            | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern                                       | All negative                                                                           |
| Herpes simplex I    | 18 AD<br>5 Controls<br>6 AD<br>2 Controls | Cerebral cortex<br>Substantia<br>innominata | Southern<br>Southern                           | All negative<br>All negative                                                           |
| Herpes simplex II   | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern                                       | All negative                                                                           |
| Adenovirus 2        | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern                                       | All negative                                                                           |
| SV <sub>40</sub>    | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern                                       | All negative                                                                           |
| Hepatitis B         | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern                                       | All negative                                                                           |
| Poliovirus          | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern,<br>Dot blot                          | All negative<br>All negative                                                           |
| Influenza A         | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern,<br>Dot blot                          | All negative<br>All negative                                                           |
| Influenza B         | 18 AD<br>5 Controls                       | Cerebral cortex                             | Southern,<br>Dot blot                          | All negative<br>All negative                                                           |
| Measles             | 18 AD<br>5 Controls<br>6 AD<br>2 Controls | Cerebral cortex<br>Substantia<br>innominata | Southern,<br>Dot blot<br>Southern,<br>Dot blot | All negative<br>All negative<br>All negative<br>1 positive<br>control<br>1 positive AD |

innominata when c-DNA from measles virus was used as a probe; one was from a control brain and the other from an AD brain (data not shown). In spite of the fact that these 2 samples were positive in duplicate trials, the significance of these results is at present unclear.

### *Specific Viral Antigens*

Four specific areas in each of 8 AD brains and 5 controls were tested with 8 viral probes (3 DNA and 5 RNA viruses). There was no positive reproducible specific reaction between the tissue sections and the immune sera.

## DISCUSSION

The recent advances in molecular biology such as the use of restriction enzymes, Southern blotting and hybridization with highly labelled probes produced by nick-

translation, provide very sensitive techniques to detect viral sequences that may occur at less than one copy per cell in infected tissues. With these new tools it was possible to detect the presence of HSV type 1 DNA in human brain tissue (Fraser *et al.*, 1981), of varicella-zoster virus DNA in human sensory ganglia (Gilden *et al.*, 1983) and of Epstein-Barr virus DNA in CNS lymphoma (Hochberg *et al.*, 1983). Furthermore, the presence of measles virus nucleotide sequences was also detected by using a highly labelled probe that hybridized in situ to cells from brain tissues from patients with subacute sclerosing panencephalitis and multiple sclerosis (Haase *et al.*, 1981).

The DNA and RNA viruses used in our current studies were chosen because of the large spectrum of diseases that they cause in humans. SV<sub>40</sub>, although a monkey virus, was included because of its close homology to the human JC virus, the agent in PML. Additionally, such viruses as polio, measles, herpes and CMV are important pathogens of the CNS, and the influenza virus has been suggestively implicated in encephalitis. Our findings confirm and extend the recent report of Taylor *et al.* (1984) in which a herpes simplex type 1 DNA was employed as a probe in brains of AD using spot dot hybridization. The studies reported here using Southern blotting and hybridization with highly radioactive probes provide a better system of detection since these techniques allow the probing of smaller size restriction fragments in digested brain DNA. The results, although negative, do not exclude the possibility that conventional viruses may play a role in the aetiology and pathogenesis of AD. The specific viruses chosen in this study may not be the ones involved in the disease. At the time of death, the brain areas selected may have been too damaged, so that cells or foci of cells that may have contained viral sequences or expressed viral antigenic determinants may have disappeared from the CNS. Thirdly, although most unlikely, the level of detection may not be sensitive enough.

We did find a positive signal (duplicate trials) in the RNA extracted from the substantia innominata when c-DNA from measles virus was used as a probe, in both a control brain and an AD brain; this finding, by itself, does not exclude a viral cause for the disease process, although its significance at present remains uninterpretable. It is worth mentioning that in two other studies viral nucleic acid sequences had been detected in CNS tissues for which there was no convincing reasonable explanation. Thus picornavirus sequences were detected by in situ hybridization in motor cortex and spinal cord of a patient with amyotrophic lateral sclerosis and of 1 control case (Brahic *et al.*, 1985), and cytomegalovirus DNA was detected by dot blot technique in 1 control brain out of 83 brains studied from cases of Huntington's chorea, schizophrenia and controls (Taylor *et al.*, 1985).

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# FOCAL ISCHAEMIA CAUSED BY INSTABILITY OF CEREBROVASCULAR TONE DURING ATTACKS OF HEMIPLEGIC MIGRAINE

## A REGIONAL CEREBRAL BLOOD FLOW STUDY<sup>1</sup>

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### SUMMARY

During the course of hemiplegic migraine in 3 patients, changes in regional cerebral blood flow (rCBF) were recorded by the intracarotid <sup>133</sup>Xe method and a 254 multidetector camera covering one hemisphere. The rCBF measurements were performed in conjunction with cerebral angiography. During repeated rCBF measurements all 3 patients developed focal hypoperfusion originating in the frontal lobe, subsequently spreading posteriorly to involve the precentral and postcentral regions. In 2 cases focal hyperperfusion appeared to precede the hypoperfusion. In association with the rCBF changes the patients developed transient motor and/or sensory deficits and subsequently severe headache. No signs of arterial occlusion were found.

In the over and underperfused regions blood flow fluctuated rapidly because of instability of cerebrovascular tone, defined as transient constriction of the smallest cerebral vessels (arterioles) alternating with a normal calibre for these vessels and/or short periods of vasodilatation. It is considered to be a primary pathological condition of the vessels.

When vasoconstriction was present the blood flow decreased to values consistent with ischaemia, which was probably the cause of the neurological deficits. On the basis of these observations and previous work from our laboratory we conclude that instability of cerebrovascular tone may cause focal ischaemia during the course of attacks of classical and hemiplegic migraine.

### INTRODUCTION

Recordings of regional cerebral blood flow (rCBF) have contributed important information on the marked changes in regional cortical blood supply seen during attacks of migraine. Focal hypoperfusion in the posterior parts of the cerebral cortex has been described in connection with attacks of classical migraine (Skinhøj,

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1973; Olesen *et al.*, 1981; Lauritzen *et al.*, 1983; Olsen *et al.*, 1987). Probably in all cases repeated flow values were so low in these hypoperfused areas that it has been suggested that ischaemia is the primary cause of the neurological deficits associated with migraine (Olsen *et al.*, 1987). The appearance of visual and sensory deficits in association with attacks of classical migraine can be explained by hypoperfusion originating in the occipital lobe, spreading forwards to the parietal and temporal lobes, inducing transient ischaemia in these brain regions.

Hemiplegic migraine is classified as migrainous headache associated with motor and/or sensory deficits, which can persist during and after the headache (Ad hoc Committee on Classification of Headache, 1962). Hemiplegic migraine is not necessarily associated with well defined visual prodromes. We have examined 3 patients with a history of hemiplegic migraine. During repeated rCBF measurements all patients developed a focal hypoperfusion in the frontal lobe. The hypoperfusion subsequently spread posteriorly to involve a major part of the frontal lobe and, in 2 cases, the parietal lobe. The patients developed transient sensory and motor symptoms and subsequently severe headache.

## METHODS

Puncture of the common carotid artery was performed under local anaesthesia and cerebral angiography undertaken by administering the contrast medium through a cannula. By the Seldinger technique we introduced a small soft polyethylene catheter into the internal carotid artery after cerebral angiography. We then measured rCBF with the intracarotid  $^{133}\text{Xe}$  method and a 254 detector gamma camera covering one hemisphere. This method has previously been used by Olesen *et al.* (1981) and Lauritzen *et al.* (1982) in the examination of patients with classical migraine. The equipment and method has been described elsewhere (Olesen *et al.*, 1971; Sveinottir *et al.*, 1977; Larsen *et al.*, 1978).

During each rCBF measurement a bolus of 5 to 10 mCi of  $^{133}\text{Xe}$  dissolved in 5 ml of saline was injected through the catheter. The  $^{133}\text{Xe}$  wash-out was registered by the camera and the data processed on-line in a digital computer. The data were visualized on a colour TV monitor (*see fig. 1*); the calculated values could be obtained from a printer.

In the first 12 s after the isotope injection the sampling interval was 1/s. In this way we measured the arrival of isotope in the large intracerebral vessels and the rapid disappearance of the isotope from these vessels (Frigberg *et al.*, 1985). The very early part of the clearance curves from detectors covering the large vessels consists of vascular spikes. In the normal brain these large vessel vascular spikes are seen within the first 2 to 3 s after isotope injection and they are all terminated within 5 s as the isotope is further distributed throughout the cerebral cortex. Thus the isotope angiogram obtained during the first 5 s of measurement can be used in evaluating the arterial distribution of the isotope (Olsen *et al.*, 1981). The computer calculated rCBF as the initial slope of the logarithmically transformed  $^{133}\text{Xe}$  clearance curve obtained from 12 to 60 s after isotope injection (Olesen *et al.*, 1971).

$$\text{Blood flow} = k \cdot \lambda \cdot 100 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$$

where  $k$  is the rate constant and  $\lambda$  is the tissue-to-blood partition coefficient, which in grey matter is  $0.87 \text{ ml} \cdot \text{g}^{-1}$ .

The computer automatically corrected for background activity and remaining activity in the brain. rCBF values calculated this way almost exclusively reflect blood flow in the grey matter of the cerebral cortex. After the rCBF measurements we performed a detailed examination of the 254 clearance

curves from each study. Representative curves of different parts of the brain were plotted in a semilogarithmic diagram from count rates obtained from 0 to 120 s after isotope injection (see figs 3–5). These curves were analysed for goodness of fit and linearity by linear regression analysis.

The first and second rCBF measurements were performed with a 20 to 25 min interval, whereas the following measurements employed 10 to 20 min intervals. Simultaneously with each rCBF measurement  $p\text{CO}_2$ , mean arterial blood pressure and pulse rate were recorded through the intra-carotid catheter. The flow values were not corrected for changes in  $p\text{CO}_2$  in this study.

## PATIENTS

In the course of three years, rCBF measurements were performed on 130 patients as a supplement to cerebral angiography. During angiography and the subsequent rCBF measurement, clinical symptoms of hemiplegic migraine appeared in 3 patients. In none of the remaining 127 patients was there a history of hemiplegic migraine and in none did symptoms of hemiplegic migraine develop during the investigation.

All patients were admitted for investigation because their symptoms might have been caused by intracranial or extracranial disease amenable to surgical treatment. The 3 patients reported had had symptoms which could have been caused by cerebrovascular embolism (Cases 2, 3) or a cerebral vascular malformation (Case 1) and, for this reason, cerebral angiography was performed. Unexpectedly the 3 patients developed an attack of migraine during the rCBF measurements. It then became clear that their previous symptoms represented hemiplegic migraine.

## CASE HISTORIES AND rCBF MEASUREMENTS

### *Case 1*

Male, aged 53 yrs. The patient's grandmother, mother and mother's brother had all died from strokes when aged approximately 50 yrs. The patient's mother and 3 of her 7 siblings suffered from migraine. The patient experienced his first migraine attack at the age of 30 yrs and since then had had right-sided throbbing headaches lasting for 1 day twice monthly preceded by slight depression. Often, but not always, he experienced left-sided facial paraesthesiae before and during the headache. The headache always began with pain in the right eye. Associated phenomena that might have suggested Horton's syndrome were never present. The headache was accompanied by photo and phonophobia.

The patient was admitted because of increasing frequency of attacks of headache and examined in order to exclude an intracranial vascular malformation. A neuro-ophthalmological examination did not reveal abnormalities of the eyes or related structures. Right-sided cerebral angiography was normal and a CT scan revealed only slight cortical atrophy.

During the first measurement there was a normal resting rCBF pattern except in the superior frontal part of the frontal lobe, where there was focal relative hyperperfusion with mean flow of  $56 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  (fig. 1). This was 40% above the rCBF in the area in the unaffected brain, seen during the fifth flow measurement. During the second rCBF measurement a focal hypoperfusion appeared in the previously hyperperfused area. The hypoperfusion subsequently spread posteriorly. During the fourth measurement a mean flow  $17.8 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  was present in a major part of the frontal and parietal lobes, and the patient developed left-sided facial paraesthesiae lasting for 1–2 h. A normal rCBF pattern was restored at the time of the final examination. Just after termination of the measurements the patient developed intense pain behind the right eye, followed by throbbing headache and vomiting.

*Case 2*

A 67-year-old man with a 40 yr history of attacks of bilateral throbbing headache. The patient's daughter had suffered from classical migraine since childhood. The patient usually had a sensation of diffuse weakness of the whole body before his migraine attacks, which always started with pain behind both eyes. He never experienced associated visual disturbances. Several examinations by ophthalmologists had revealed no abnormalities.

In the 3 yrs before admission, the patient developed left-sided hemiparesis of short duration in connection with his migraine attacks. He was admitted to hospital after his fourth attack of hemiparesis and severe headache. The neurological symptoms disappeared within a few hours. On the third day after admission right-sided cerebral angiography and rCBF measurements were performed.

The cerebral angiogram showed arteriosclerotic changes in extracerebral and intracerebral vessels, but no occlusions. A CT scan was not performed. During the rCBF measurements the patient's cerebration became slow and he developed a left-sided hemiparesis which persisted for less than 6 h.

The rCBF pattern during the first measurement was normal. Hypoperfusion began during the 25 min interval between the first and second measurements and covered most of the frontal lobe at the time of the second measurement. Mean flow in the focal frontal hypoperfused cortex was  $21.1 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ . During the third and fourth rCBF measurements the hypoperfused area diminished to a small area in the frontal lobe and the total mean hemisphere blood flow was slightly reduced as compared with the initial normal rCBF pattern.

*Case 3*

A male aged 75 yrs. His mother and 2 sisters suffered from migraine. He experienced his first migraine attacks 30 yrs before the present examination. Twice monthly he suddenly had the sensation that he did not know where he was and had a feeling of not knowing what he was doing. At that time he worked as a chauffeur and when he was struck by an attack during his work, he felt completely unable to drive, he left his car and went home. These prodromes were subsequently accompanied by intense pain behind the right eye, developing into right-sided throbbing headache, photo- and phonophobia and vomiting. There were never visual disturbances before or during the attacks.

The attacks, as described above, recurred for 2 yrs and then disappeared spontaneously, although sporadic attacks of pain behind the right eye or both eyes persisted.

Before the present examination the patient within 3 months had 2 attacks as described above, but now associated with left-sided hemiparesis and left-sided facial paraesthesiae. He was admitted to hospital shortly after his second attack and the neurological symptoms recovered within a few hours. The day after admission right-sided cerebral angiography and rCBF measurements were performed. The cerebral angiogram revealed varying calibre in the intracranial and extracerebral vessels, but no visible atheromatous plaques or occlusions. A CT scan showed cortical atrophy.

Mean cerebral blood flow was low, commensurate with the age of the patient. During the first measurement there was a normal rCBF pattern. At the time of the second, focal relative hyperperfusion with mean flow of  $51 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  appeared in the frontal lobe. This is 60% above rCBF in this area when compared with the normal first rCBF pattern. During the third measurement, it was observed that the area previously hyperperfused was now replaced by focal hypoperfusion. Subsequently the hypoperfusion spread posteriorly covering most of the frontal and parietal lobes at the time of the fifth measurement. Mean flow in the hypoperfused area was  $12.4 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  when the migraine attack appeared during the fifth rCBF measurement and the patient could not tolerate further examination beyond this point because of intense throbbing headache and vomiting. Simultaneously with the appearance of hypoperfusion, the neurological deficits that had occurred previously developed and persisted for 12 to 18 h.

## RESULTS

No signs of arterial occlusion were seen, either on the cerebral angiograms or on the separate isotope angiograms obtained during each rCBF measurement. The isotope angiograms showed a homogeneous isotope distribution throughout the examination in each patient. During repeated rCBF measurements all patients developed a spreading cortical hypoperfusion originating in the frontal lobe (fig. 1). The mean hemispheric blood flow and corresponding  $p\text{CO}_2$  are given in Table 1. Table 2 shows the mean rCBF values of the regions of interest as calculated from 12 to 60 s after the isotope injection. The description of the clinical events and rCBF changes have been given in the case histories in the previous section. Fig. 2 is a schematic illustration of the localization of the hyper- and hypoperfused areas. During the three series of rCBF measurements mean arterial blood pressure and pulse rate were normal and varied only within 10 mmHg and 16 beats/min, respectively. All patients recovered completely from their symptoms.

*The  $^{133}\text{Xe}$  Clearance Curves*

Initially all the full length clearance curves (12–120 s) were assumed to be linear after logarithmic transformation. After performing linear regression analysis the residual variances were plotted for each curve.

In all the normal perfused brain regions which were not affected by hyper- or hypoperfusion, the plotted residuals were clearly symmetrically distributed, indicating stable (linear) wash-out rates throughout the measurements. In the brain regions in which hyper- or hypoperfusion appeared during the 4 or 5 sequential rCBF measurements, symmetric distributions of the plotted residuals and constant linear clearance curves were found as long as there were normal flow values in these regions. But when the rCBF pattern showed that hyper- or hypoperfusion had developed, the plots of the residuals from the affected curves became highly asymmetrically distributed in relation to the curve. This indicates that in these curves the assumption of linearity was wrong and that the detectors situated above the affected regions recorded unstable (nonlinear) clearance curves. As can be seen from figs 3, 4 and 5, the unstable clearance curves were characterized by a fluctuating slope during the course of the individual measurements. Each of these unstable full length curves could be subdivided into 2 to 5 linear components.

The rate constants and blood flow values were calculated from each of the linear components of the curves. The correlation coefficients were in the range of  $-0.75$  to  $-0.99$ , in most cases closer to the latter value. In this way it could be demonstrated that the unstable clearance curves reflected fluctuating blood flow: extremely low rCBF values ( $0\text{--}20\text{ ml}\cdot 100\text{ g}^{-1}\cdot\text{min}^{-1}$ ) were seen in several intervals of 20 to 60 s, alternating with short intervals of normal blood flow or in some cases even hyperaemic flow values ( $70\text{--}120\text{ ml}\cdot 100\text{ g}^{-1}\cdot\text{min}^{-1}$ ). We have termed the pathological condition of the cerebral vessels causing these fast fluctuations of rCBF *instability of cerebrovascular tone*.

The time of arrival of the isotope in the tissue could be estimated from the very early part of each curve. During all rCBF measurements the maximum count-rate was found within 3 to 4 s after the isotope injection. The significance of this finding will be considered in the Discussion.

## DISCUSSION

Several authors have reported that classical migraine is associated with hypoperfusion originating in the posterior parts of the brain (Skinhøj, 1973; Hachinski *et al.*, 1977; Olesen *et al.*, 1981; Lauritzen *et al.*, 1983). The hypoperfusion can subsequently involve the pre- and postcentral cortical areas. Neurological symptoms before and during an attack of classical migraine, such as prodromal scintillations, scotomas and hemianopia followed by paraesthesiae and in some cases hemiparesis, without doubt arise from the cortical areas affected by the hypoperfusion.

The rCBF examination of the patients reported here demonstrates for the first time that migraine-associated hypoperfusion may originate in the frontal lobe. The hypoperfusion spread posteriorly and in these 3 cases the motor cortex was involved. In 2 patients (Cases 1, 3) part of the parietal lobe was also involved. The patients all developed motor and/or sensory symptoms as the pre- and postcentral cortex was hypoperfused. The occipital cortex was not affected by hypoperfusion. The patients had never experienced visual prodromes in connection with their previous attacks and during the current examinations visual symptoms were also absent. Further, the neurological deficits persisted during the headache. For these reasons the attacks may be classified as *hemiplegic migraine* (Ad hoc Committee on Classification of Headache, 1962).

### *Focal Ischaemia*

In a study of cerebral blood flow in patients with classical migraine, Olsen *et al.* (1987) concluded that focal cortical ischaemia in the posterior parts of the brain was present during the prodromal phase of an attack. Complete inhibition of the neuronal activity in the human cerebral cortex by intracarotid injection of a GABA agonist 4,5,6,7-tetrahydroisoxazolom(5,4-c)-pyradine-3-ol (THIP), decreased the metabolism and blood flow to  $22 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  (Roland and Friberg, 1983). Thus cortical blood flow around  $22 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  must be considered a basic level sufficient to supply the cells of the cortex during a 'vegetative' state. When CBF is reduced below  $23 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  during carotid clamping in patients undergoing carotid endarterectomy the EEG waves diminish (Trojaborg and Boysen, 1973). In patients suffering from transient ischaemic attacks a CBF of  $22.1 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  has been reported as the lowest value consistent with normal cerebral function (Powers *et al.*, 1984). In the awake monkey neurological deficits appear when experimental occlusion of the middle cerebral artery causes a CBF decrease below  $23 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  (Jones *et al.*, 1981). In a single unit activity

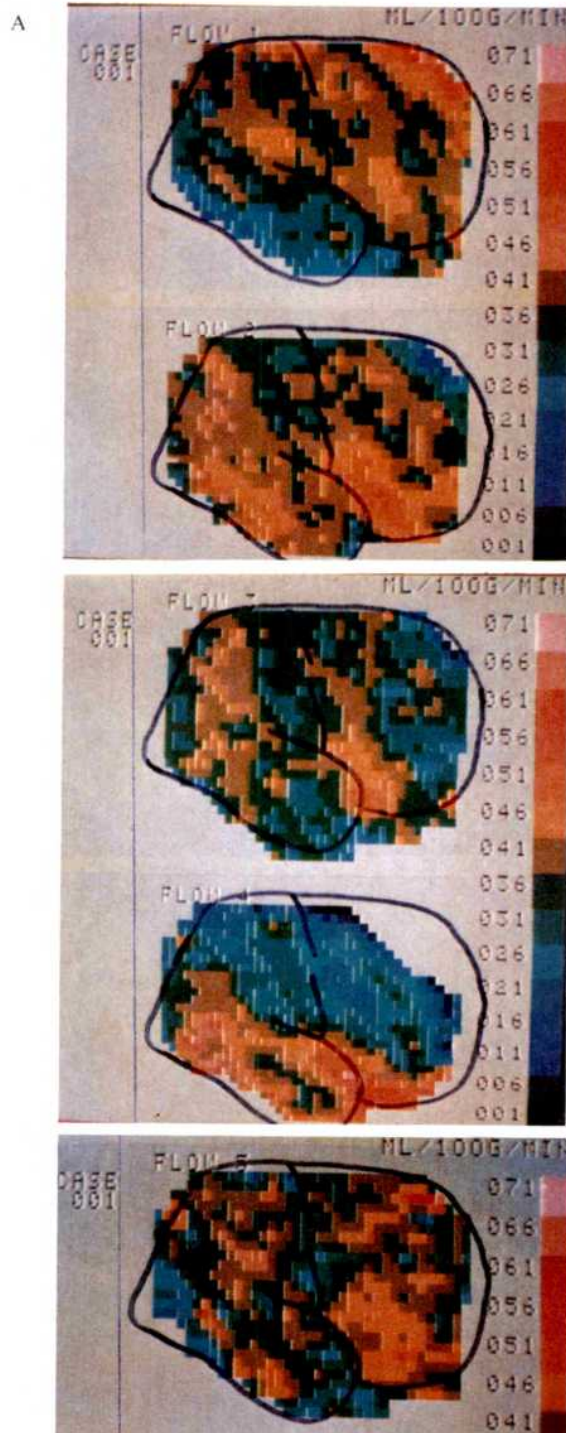
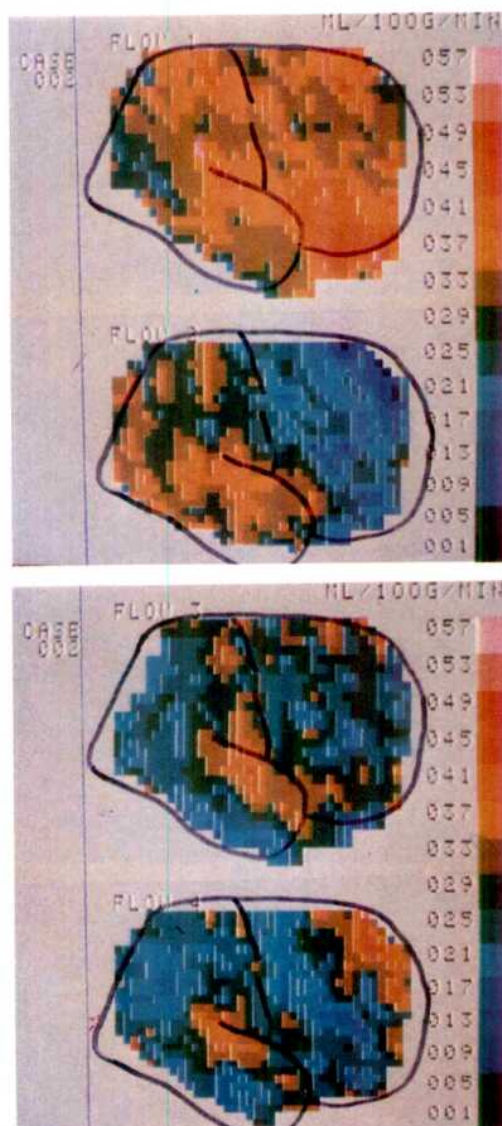


FIG. 1. rCBF patterns obtained from the individual measurements. rCBF is expressed in  $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ . A, Case 1; B, Case 2; C, Case 3.

B

FIG 1. *Contd.*



C

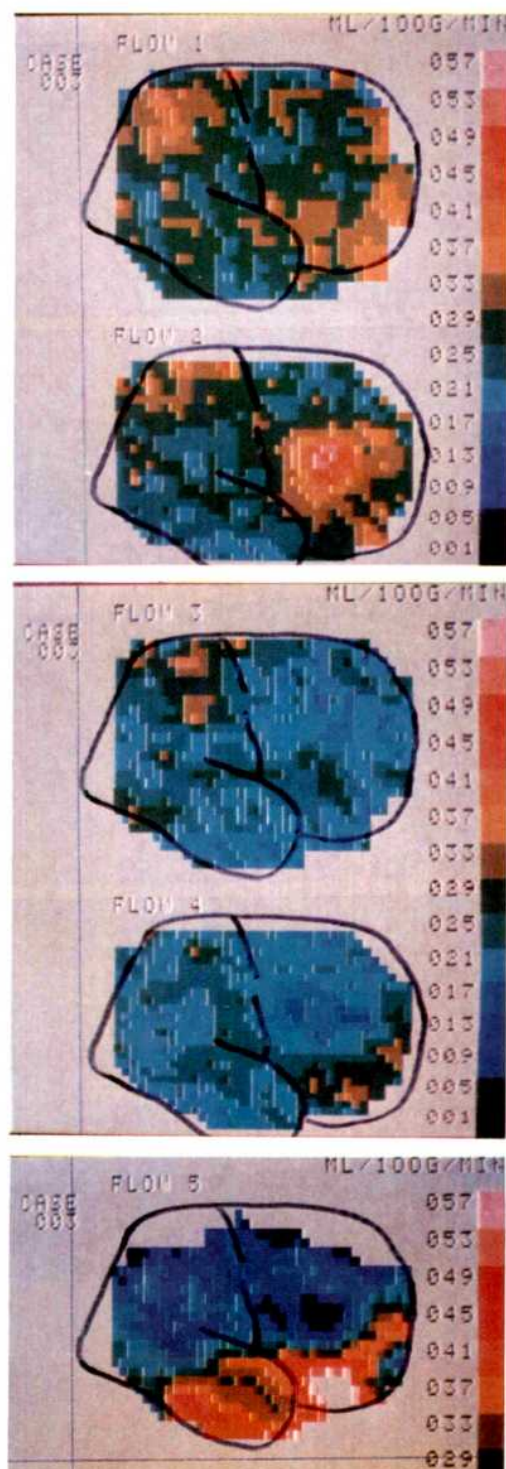
FIG 1. *Contd.*

TABLE 1. MEAN HEMISPHERE CORTICAL BLOOD FLOW AND ARTERIAL  $p\text{CO}_2$  VALUES.  $r\text{CBF}$  VALUES CALCULATED FROM 12–60 s AFTER ISOTOPE INJECTION

|        | <i>Flow no.</i> | <i>rCBF ml <math>\times</math> 100 g<sup>-1</sup> <math>\times</math> min<sup>-1</sup></i> | <i>pCO<sub>2</sub> mmHg</i> |
|--------|-----------------|--------------------------------------------------------------------------------------------|-----------------------------|
| Case 1 | 1               | 40                                                                                         | 37.6                        |
|        | 2               | 43                                                                                         | 38.4                        |
|        | 3               | 39                                                                                         | 39.1                        |
|        | 4               | 37                                                                                         | 39.3                        |
|        | 5               | 40                                                                                         | 39.4                        |
| Case 2 | 1               | 37                                                                                         | 35.5                        |
|        | 2               | 30                                                                                         | 35.0                        |
|        | 3               | 29                                                                                         | 35.0                        |
|        | 4               | 28                                                                                         | 35.1                        |
| Case 3 | 1               | 31                                                                                         | 40.7                        |
|        | 2               | 31                                                                                         | 40.2                        |
|        | 3               | 26                                                                                         | 41.7                        |
|        | 4               | 25                                                                                         | 41.2                        |
|        | 5               | 25                                                                                         | 39.2                        |

TABLE 2. MEAN  $r\text{CBF}^*$  IN THE RELATIVE HYPERAEMIC AND ISCHAEMIC AREAS AND MEAN  $r\text{CBF}$  IN THE CORRESPONDING AREAS IN THE UNAFFECTED BRAIN

|        | <i>Focal relative hyperaemia</i> | <i>During ischaemia</i> | <i>Before/after ischaemia</i> |
|--------|----------------------------------|-------------------------|-------------------------------|
| Case 1 | 56.1                             | 17.8                    | 44.8                          |
| Case 2 | —                                | 21.1                    | 38.4                          |
| Case 3 | 51.2                             | 12.4                    | 30.8                          |

\*  $r\text{CBF}$  values in  $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  are calculated from 12–60 s after isotope injection.

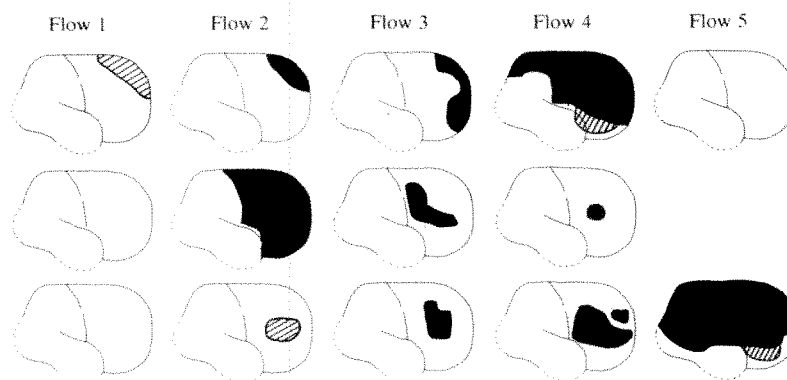


FIG. 2. Outline of the hyper- and hypoperfused areas. Hatched and black areas represent, respectively,  $r\text{CBF}$  values 40% and 20% below mean flow in the areas in the unaffected brain. *Case 1*, top row; *Case 2*, middle row; *Case 3*, bottom row.

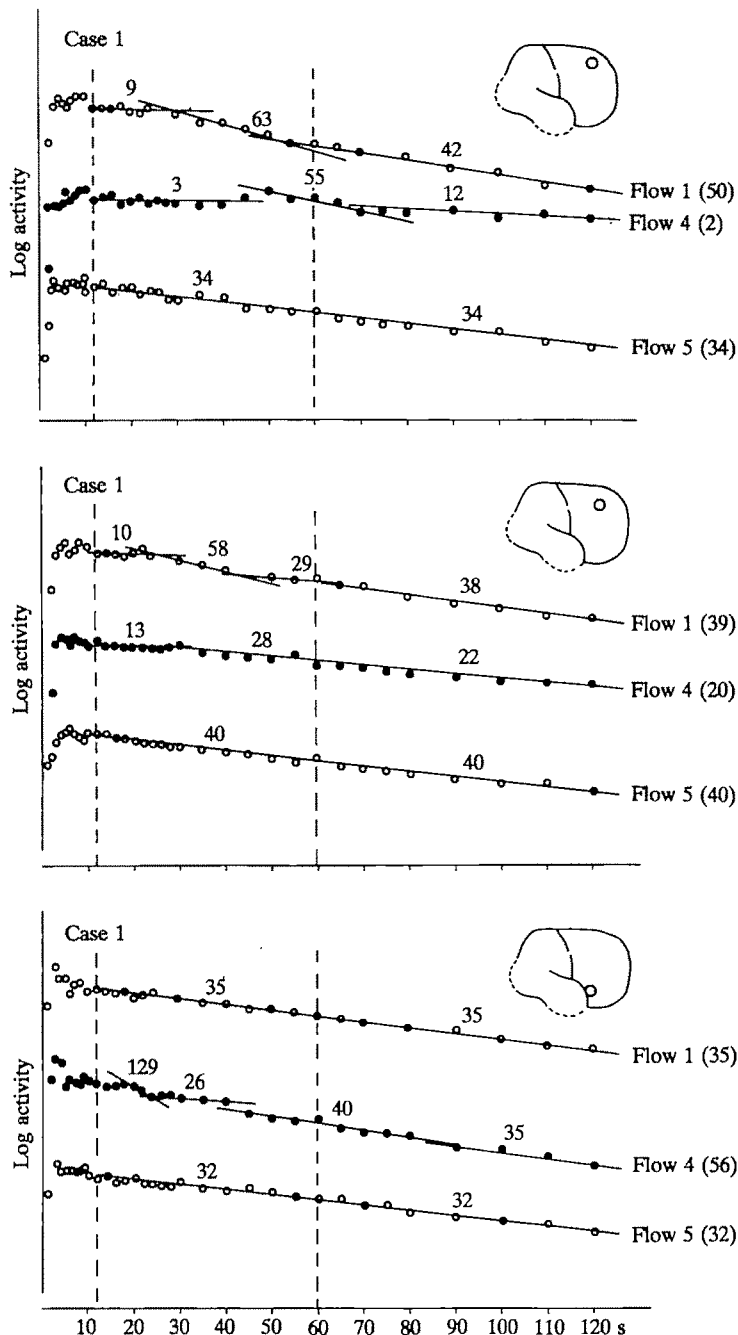
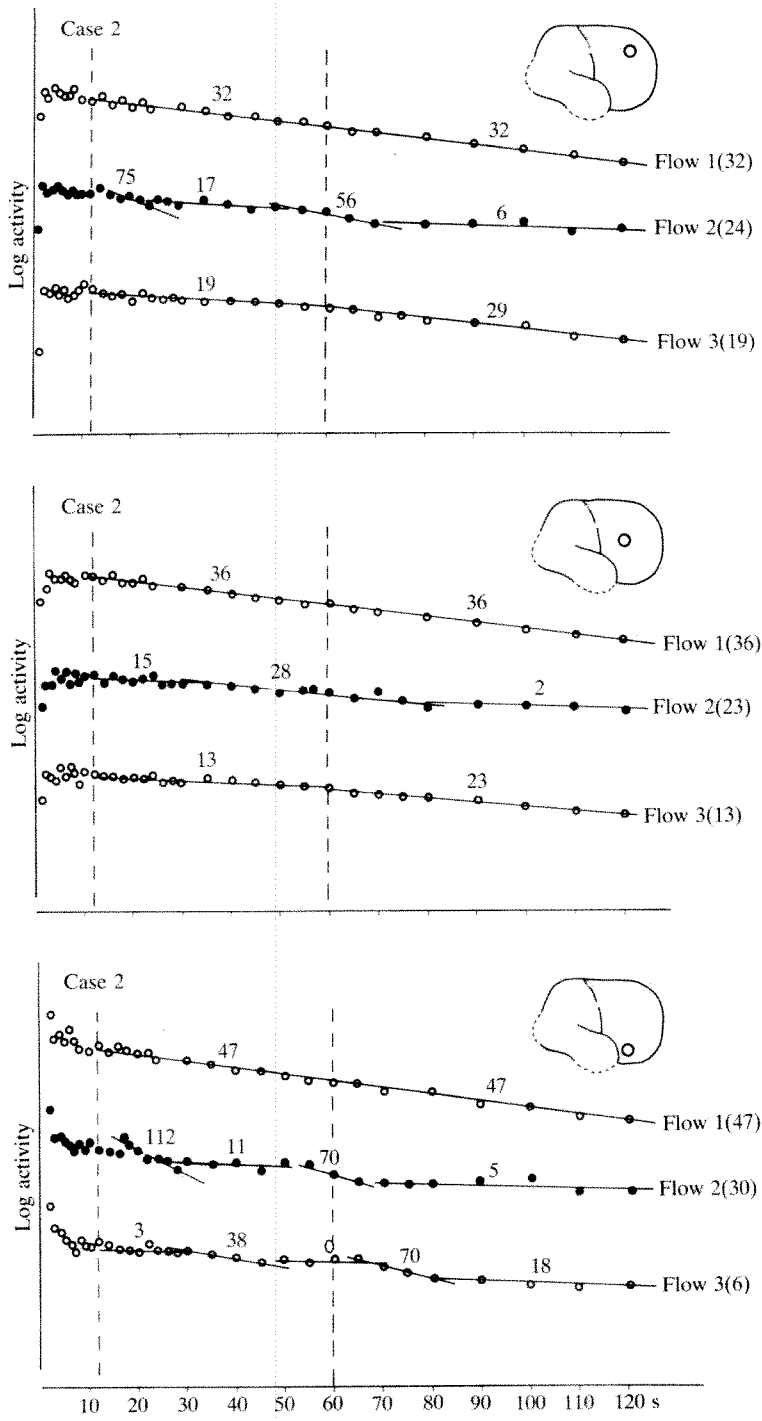


FIG. 3. (and, on following pages) Figs 4 and 5. The logarithmically-transformed  $^{133}\text{Xe}$  clearance curves recorded with single detectors over a period of 120 s after isotope injection for *Case 1* in fig. 3, *Case 2* in fig. 4 and *Case 3* in fig. 5. The activity was measured in counts/s; the maximum number of counts was approximately the same in each study. For illustrative purpose the curves in each diagram have been displaced.

The position of the detectors is illustrated as circles on the brains in the upper right corner of each diagram. The figures appearing just above the individual linear intervals of the curves indicate blood flow calculated from each part of the curves. The flow number is noted to the right of each curve and the figures in brackets indicate the flow values from 12–60 s of the clearance curves (dotted lines) calculated by the computer. Comparison of the clearance curves from each detector position with the rCBF patterns (figs 1, 2) shows that the clearance curves were linear when regional blood flow was normal, but became unstable when hyper- or hypoperfusion was present. In both cases, intervals of ischaemic flow values are seen.



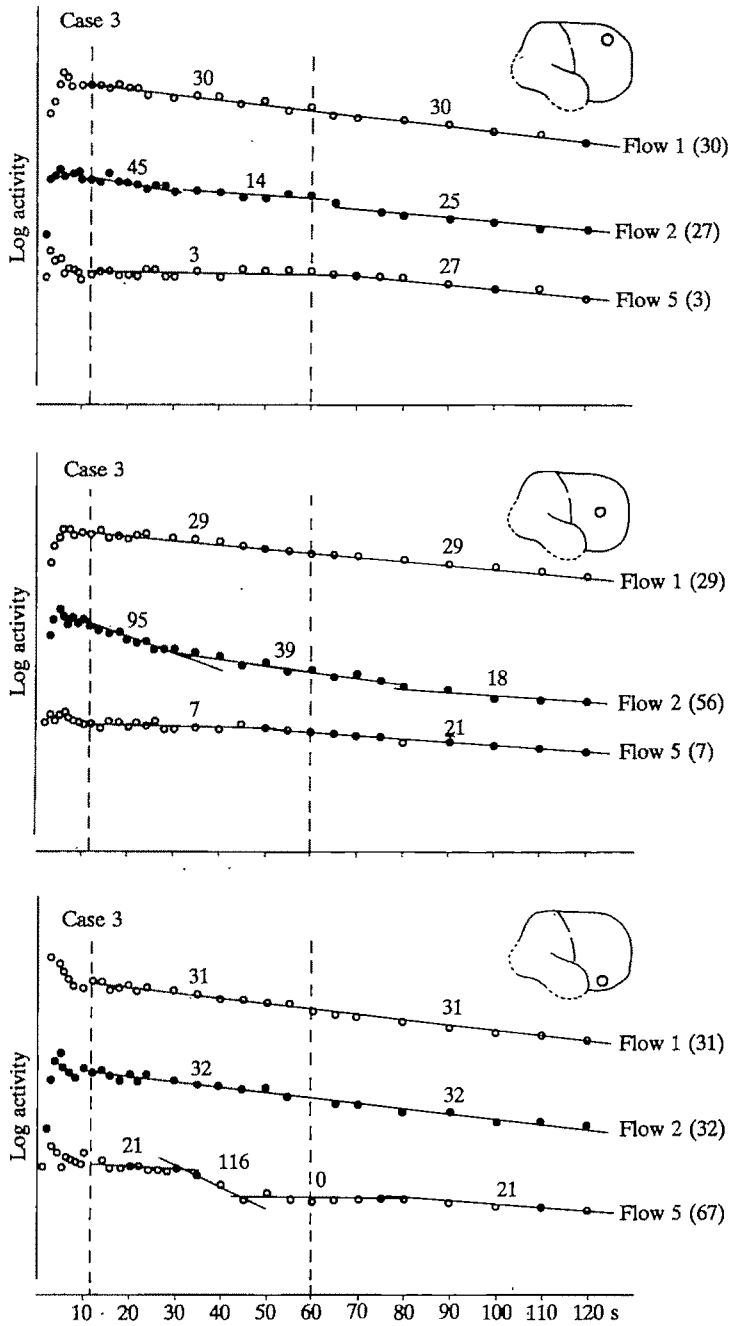


FIG. 5.

study, Heiss *et al.* (1976) found that some neurons discontinued their spontaneous activity when CBF decreased below  $23 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ .

When CBF decreases further to values of  $15\text{--}18 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  the evoked potentials of the cat and monkey are completely suppressed (Branston *et al.*, 1974; Heiss *et al.*, 1976) and the EEG gradually becomes isoelectric in man (Trojaborg and Boysten, 1973).

Results from the studies mentioned above indicate that CBF below  $21\text{--}23 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  are insufficient for normal cortical function. However, cortical blood flow in the interval  $18\text{--}23 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  may be tolerated for several weeks without causing cell death, whereas cortical blood flow below  $15\text{--}17 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  is followed by cell death within 4 to 8 h (Jones *et al.*, 1981).

In our study we found that the mean rCBF values in the hypoperfused regions were  $12\text{--}21 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ . The mean rCBF values were calculated from 48 s intervals from the unstable clearance curves. The results presented here show that in short intervals within these 48 s the blood flow was reduced even below the calculated mean rCBF values.

We conclude that flow values consistent with ischaemia were present in the hypoperfused parts of cortex and that ischaemia most probably is the cause of the neurological deficits associated with hemiplegic migraine. We suggest that the severity and duration of the neurological symptoms associated with hemiplegic migraine are proportional to the number and duration of periods in which ischaemic flow values are present, as well as being related to the degree of reduction in flow.

The isotope angiograms showed a normal temporal and spatial isotope distribution in the main arteries of the brain (Friberg *et al.*, 1985). Further, the isotope angiograms were without signs of occlusions as described by Olsen *et al.* (1981). We consider that the combination of the unstable clearance curves, the localization and the spreading pattern of hypoperfusion, the absence of x-ray angiographic and isotope angiographic signs of occlusion exclude transient arterial occlusion due to embolism.

### *Instability of Cerebrovascular Tone*

Figs 3, 4 and 5 give a few examples of how we have divided the unstable clearance curves into discrete linear components. The statistical validity of the calculated flow values depends on the number of samples, the sampling intervals and the count rate. The mean intervals of sampling were 32 s, ranging from 8 to 70 s. However, only less than 10% of the components indicated were shorter than 15 s. The lowest (ischaemic) blood flow values were in all cases calculated from the longer linear components. In a few cases we have suggested that relatively high blood values could be calculated from very short components. Clearly the accuracy of these cannot be as good as that of the lower blood flow values calculated from much longer sampling intervals. Even though in this way we may have made errors in calculation of the exact magnitude of these high flow values, they were without doubt much higher and differed significantly from flow values calculated from

neighbouring components. We have therefore found it reasonable to suggest that the unstable clearance curves reflect extremely fluctuating blood flow. It should be emphasized that unstable clearance curves are a highly abnormal finding when using this method and that strictly linear clearance curves have been the general finding in the examination of more than 500 patients in our department.

We think that the results reported here suggest that a condition of *instability of cerebrovascular tone* was present in the vessels in the hypoperfused areas of the brain. Instability of cerebrovascular tone instability was characterized by fast fluctuations in blood flow in the affected brain regions, causing several intervals of low flow values consistent with ischaemia, alternating with intervals of normal and/or hyperaemic flow values.

The clearance curves showed that the isotope was distributed throughout the examined hemisphere within the first 3 to 4 s after the intra-arterial bolus injection. Further, during different measurements in the same brain region, the maximum count rate was obtained within approximately the same time interval irrespective of normal blood flow or hypoperfusion being present (figs 3–5). We therefore, suggest that instability of cerebrovascular tone only involves regional constriction and dilatation of the smallest vessels of the brain, as constriction of the large arteries would have caused a markedly delayed arrival of the isotope and a distinctly abnormal isotope distribution would have been seen on the isotope angiogram.

Instability of cerebrovascular tone can thus be defined as transient constriction of the smallest cerebral vessels (arterioles) alternating with normal calibre of these vessels and/or short periods of vasodilatation. When constriction is present blood flow decreases to values consistent with ischaemia.

When intervals of vasodilatation occurred during the 48 s period from which the mean rCBF values were calculated by the computer, it appeared from the flow pattern that relative hyperperfusion was present throughout the 2 min measurement. But the plotted unstable clearance curves, examples of which are given in figs 3–5, showed that ischaemic flow values could also occur in the regions which at first were regarded as hyperperfused (fig. 2). In several cases Olesen *et al.* (1981) also observed focal hyperaemia proceeding the posterior hypoperfusion associated with classical migraine. Our results may indicate that irrespective of the flow patterns showing focal hyperperfusion or hypoperfusion, the same phenomenon of instability of cerebrovascular tone is reflected. The same phenomenon of instability of cerebrovascular tone was also seen during the prodrome phase of attacks in the patients suffering from classical migraine reported by Olsen *et al.* (1987) (unpublished observations by the authors).

The course of the smallest cerebral arteries and arterioles is perpendicular to the brain surface. These vessels supply blood to the cortex as well as to the underlying white matter. When cortical ischaemia was present in the examined patients, hypoperfusion of the underlying white matter would also be suspected. This was confirmed in our results, as the lowest flow values seen during cerebrovascular tone instability exceeded the value of  $20 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  normally found in white

matter (Lassen *et al.*, 1983). This is true even when these low flow values are calculated using the tissue-to-blood partition coefficient of white matter,  $\lambda = 1.50 \text{ ml} \cdot \text{g}^{-1}$  (Lassen *et al.*, 1983).

### *The Cause of Instability of Cerebrovascular Tone*

The size of the hypoperfused regions was not constant, but increased or decreased (fig. 2). This gave an impression of a spreading pattern of hypoperfusion not respecting the territories of the major cerebral arteries. A pattern of a spreading hypoperfusion in the posterior parts of the brain associated with classical migraine was also found by Olesen *et al.* (1981) and by Lauritzen *et al.* (1983) and Lauritzen and Olesen (1984). They suggested that the hypoperfusion progressed over the surface of the cortex at a rate close to 2 mm/min and that it was arrested by the primary sulci.

The results of our present studies did not confirm these suggestions. In the patients presented here, as well as in the cases of classical migraine recently reported (Olsen *et al.*, 1987), the hypoperfused regions either appeared very suddenly or were built up with individual and unpredictable speed. It was not possible to determine the exact speed of the border of the spreading hypoperfusion since we had no individual information as to the exact extent of the cortical surface, which is an extremely folded structure. Further, it could obviously be seen from the flow patterns that the spreading hypoperfusion did not respect brain surface features such as major sulci or cytoarchitectonic borders. Instead, the hypoperfusion passed freely across these borders. In our studies we have found evidence of episodic ischaemia whereas Olesen *et al.* (1981) and Lauritzen *et al.* (1983, 1984) suggested that the reduction in blood flow was not of a magnitude sufficient to cause ischaemia. On several essential points, therefore, our findings are not in accordance with the theory that spreading depression of Leão could be the cause of focal hypoperfusion preceding an attack of migraine (Lauritzen *et al.*, 1983; Lauritzen and Olesen, 1984). On the basis of our results we suggest that instability of cerebrovascular tone is primarily a pathological condition affecting blood vessels.

As was also suggested by Olesen *et al.* (1981) we think that it is very possible that the vascular changes and the migraine attacks were triggered off by one or several of the procedures performed in connection with the rCBF measurement: by the injection of local anaesthetic close to the carotid artery, by the carotid puncture, by cerebral angiography, by the indwelling catheter or by the injection bolus of isotope solution at room temperature. Nevertheless, the specific vascular changes described in this article are seen mainly in patients with migraine. Further, the neurological deficits and headache appearing in connection with the rCBF measurements were identical to the symptoms previously experienced by the patients. It is likely that the changes in cerebral blood flow occurring during a spontaneous attack are identical to those observed during measurement of rCBF.

It can only be speculated as to which biochemical processes might be involved in eliciting the phenomenon of instability of cerebrovascular tone. A number of



vasoactive substances released from perivascular nerves or thrombocytes might be suspected of being able to provoke the condition (Amery, 1982).

### *Vascular Headache*

Headache is a common symptom which can occur in isolation or appear in connection with a multiplicity of diseases (Ad hoc Committee on Classification of Headache, 1962). There are many other provocative factors other than transient cerebral ischaemia. The exact pathophysiological mechanisms of headache are not known.

In our cases of hemiplegic and classical migraine, the headache followed the focal ischaemia assumed to occur during cerebrovascular tone instability. It could be that the headache in these cases was provoked by ischaemia. It has been reported that headache is a frequent symptom encountered in association with transient ischaemic attacks (Medina *et al.*, 1975), and Fisher (1980) even suggested that late-life migraine accompaniments could represent one cause for transient ischaemic attacks.

A common feature of all the patients of this study was the description of intense pain behind one or both eyes that preceded the throbbing headache. The initial retrobulbar pain without visual deficits may be a valuable clinical feature in the diagnosis of the symptoms and rCBF changes that we have described.

### ACKNOWLEDGEMENT

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# DISORDERED AUDITORY SHORT-TERM MEMORY IN MAN AND EVENT-RELATED POTENTIALS

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## SUMMARY

Four patients with conduction aphasia and impaired auditory but relatively preserved visual digit spans were tested in a task of short-term memory, a digit probe identification task, in both the visual and auditory modalities. Five age-matched normal subjects served as controls. Behavioural measures of response accuracy and reaction time and scalp derived event-related potentials were determined as a function of the number of items to be remembered. These measures were also recorded in a task requiring the detection of infrequent stimuli ('oddball' paradigm). The patients' performance and event-related potential wave forms for the 'oddball' task were no different from those of the controls. In the digit probe identification tasks the patients showed a reduction in amplitude of a positive component at a latency of approximately 450 ms (P450) of the event-related potential to correctly identified probes in the auditory modality. This component was within normal limits with visual testing. There was an inordinate increase in the patients' reaction time to auditory but not visual stimuli when the number of items to be remembered increased from one to three. Event-related potentials were also analysed as a function of speed of reaction time, position of the matching item in the stimulus presentation set and whether the probe was correctly identified as being in-set or out-of-set. Event-related potentials associated with fast reaction times in the auditory task when a single item was presented were no different between patients and controls, indicating that patients were capable of both performing normally and generating normal potentials on some trials. The data suggest that the deficit in auditory short-term memory in these patients occurs during stimulus classification.

## INTRODUCTION

A modality-specific disorder of verbal auditory short-term memory has been proposed to account for the failure of patients with conduction aphasia to repeat short phrases, polysyllabic words or digit strings after their auditory presentation (Warrington and Shallice, 1969; Saffran and Marin, 1975; Shallice and Warrington, 1977). Otherwise these patients can have relatively preserved spontaneous speech and intellectual function without impairment of visual short-term memory or both auditory and visual long-term memory (Warrington and Shallice, 1972). The site

of this disturbance in the short-term memory system is unclear and proposals including disorders of either storage (Shallice and Warrington, 1970), a perceptual analysis system (Allport, 1984) or of response selection (Kinsbourne, 1972) have been postulated. Alterations of auditory processes are unlikely because these patients have normal memories for sequences of sounds such as barks, train whistles and thunder but not for sequences of words (Shallice and Warrington, 1974).

Event-related potentials may be relevant for helping to understand this clinical syndrome. These potentials can be recorded with relative ease from scalp electrodes using computer averaging techniques. Investigations in normal subjects have indicated that at least one of the components, a positive deflection occurring at a latency of approximately 300 ms and designated by the conventional potential nomenclature as 'P300', reflects some aspects of neural processes underlying memory. This is based on the finding that the amplitude of P300 evoked by the target in tasks in which the subject is engaged in the detection of a rare event is influenced by both its frequency of occurrence, that is, the global probability (Donchin *et al.*, 1978), as well as by subjective expectancies (Duncan-Johnson and Donchin, 1977). Moreover, there have been several studies of event-related potentials in normal subjects engaged in probe identification tasks that test short-term memory capacities in which P300 amplitude and latency change in an orderly manner as the number of items to be remembered increases (Marsh, 1975; Roth *et al.*, 1975; Gomer *et al.*, 1976; Adam and Collins, 1978; Ford *et al.*, 1979; Pfefferbaum *et al.*, 1980; Kramer *et al.*, 1986). Among the cognitive processes comprising memory, P300 seems to be associated with stimulus classification rather than response selection (Pritchard, 1981). Thus the combination of measures of P300, performance accuracy and reaction times might provide a means for attributing disorders of memory to particular stages of the memory process.

We have had the opportunity to study 4 patients fulfilling the criteria of conduction aphasia using measures of both behaviour (response accuracy and reaction time) and event-related potentials (latency and amplitude) as they engaged in a digit probe identification task presented in both auditory and visual modalities. The results provide quantitative measures that shed insights into some of the neural bases underlying the patients' disorder of auditory short-term memory.

### CASE REPORTS

Four patients with disordered auditory short-term memory were tested together with 5 healthy age-matched controls. The patients' impairment was manifested by a reduced auditory digit span and word list repetitions that were out of proportion to their other neurological deficits. Cases 1 and 2 have been described previously in papers detailing their memory and language impairments. Cases 3 and 4 have not been reported previously. The results of their Wechsler Adult Intelligence Scores

TABLE 1. NEUROPSYCHOLOGICAL TEST SCORES: AGE ADJUSTED WITH 100 AS THE MEAN

| Test                  | Patients |     |        |          |     |
|-----------------------|----------|-----|--------|----------|-----|
|                       | 1        | 2   | 3      |          | 4   |
|                       |          |     | Test a | Test b** |     |
| WAIS*                 |          |     |        |          |     |
| Verbal                | 61       | 87  | 61     | 93       | 65  |
| Arithmetic            | 4        | 8   | 2      | 10       | 4   |
| Similarities          | 7        | 11  | 6      | 8        | 4   |
| Digit Span            | 1        | 3   | 0      | 6        | 2   |
| Vocabulary            | 6        | 9   | 7      | 11       | 8   |
| Performance           | 93       | 101 | 92     | 118      | 104 |
| Picture Completion    | 9        | 9   | 7      | 11       | 9   |
| Block Design          | 7        | 7   | 12     | 13       | 7   |
| Picture Arrangement   | 10       | 12  | 3      | 14       | 14  |
| Digit Repetition      |          |     |        |          |     |
| Auditory presentation | 1        | 4   | 2      | 4        | 2   |
| Visual presentation   | 5        | 5   | 3      | 5        | 3   |

\* WAIS = Wechsler Adult Intelligence Scale. \*\* Tests a and b refer, respectively, to the initial and subsequent evaluations.

and digit repetition abilities are contained in Table 1. The patients have the common features of a reduction of their Verbal Scores compared to Performance Scores with the Digit Span being reduced out of proportion to the other tests. The number of digits they could repeat after auditory presentation was lower than after visual presentation.

#### Case 1

This patient, referred to as R.A.N. in McCarthy and Warrington (1984), is a 53-year-old right-handed man who had a sudden onset of right hemiplegia, right hemisensory loss and aphasia four years earlier due to a haemorrhage into the left parietal lobe. No specific cause for the haemorrhage was defined. The patient's deficits have gradually improved. At the time of this study he had slight right-sided weakness with marked sensory impairment involving position sense and two-point discrimination. Sharp-dull appreciation was only slightly impaired. There were no visual field deficits. His spontaneous speech was fluent with occasional phonemic and paraphasic errors. There were some naming difficulties and comprehension was good. His ability to repeat sets of digits or words was markedly impaired. The digit span to auditory presentation was between one and two items, whereas to visual presentation he could repeat correctly strings of five digits. He has had both generalized and right-sided focal sensory seizures since recovering from the acute phase of the illness that are being treated with phenytoin and phenobarbital. A CT scan at the time of this investigation showed a well-demarcated area of cerebral damage involving the left parietal lobe in the region of the angular gyrus.

#### Case 2

This patient, described as J.B., Case 2, in Warrington *et al.* (1971) is a 50-year-old right-handed woman who had a 'tennis ball sized' meningioma removed from the left temporoparietal region in

1970. Subsequently she had language difficulties which improved within a month of the operation leaving her only with an impaired ability to repeat spoken names or numbers that has also gradually improved over the intervening years. At present her auditory digit span is four items and the visual span is five items.

#### *Case 3*

This patient is a 46-year-old right-handed man who had an acute onset of language impairment three days before his being studied by us. His original deficits consisted of marked naming difficulties with only slightly impaired comprehension and spontaneous speech. There were no visual field deficits. His digit span to spoken digits was only two items and to visually presented digits three items when the first set of event-related potentials were recorded (test a). He rapidly improved and when event-related potentials were recorded again three weeks later (test b), the auditory digit span had improved to four items and the visual span to five items. Speech was fluent with only occasional naming difficulties. An MRI scan showed infarction between the posterior temporal and inferior parietal lobes.

#### *Case 4*

This patient is a 40-year-old right-handed man who had a subarachnoid haemorrhage from a left middle cerebral aneurysm two years previously. The aneurysm was clipped. On recovery from the acute phase of the illness he had a right hemiplegia and marked speech impairment. The visual fields were full. These disabilities improved so that at the time of testing there was only slight weakness of the right hand. Speech was slow with marked naming difficulties but comprehension was excellent. The auditory digit span was only two items and the visual span only three items. In all other respects he is independent in managing his life and finances. He has had generalized seizures and is currently receiving phenytoin and carbamazepine.

#### *Controls*

These were selected to be close in age to the patients and ranged from 40 to 57 years. There were 2 females and 3 males. One of the women was the wife of the first patient, one of the men was a laboratory technician in the hospital and the other 3 subjects were neurologists. Informed consent was obtained from both patients and controls participating in these experiments.

## METHODS

#### *Event-related Potential Recordings*

Silver disc electrodes were fixed on the scalp at Fz, Cz, Pz, C3, C4, P3 and P4 and each referenced to linked electrodes on the ear lobes. Eye movements were monitored by recording between electrodes above and below the right eye. Those trials containing high amplitude potentials due to eye movements were not included in the averages. The amplifier band pass was 0.01 Hz to 5 kHz. Electrical activity was sampled by the computer over a time base of 960 ms (dwell time 3.75 ms) or 1280 ms (dwell time 5.0 ms) and, in one instance in Case 1, at 1920 ms (dwell time 7.5 ms). All of the analysis times included a prestimulus baseline period of 120 ms.

#### *Experimental Paradigms*

*Detection of infrequent stimuli, the 'oddball' tasks (test a).* Event-related potentials in all the patients were recorded during the detection of an infrequent signal in both auditory and visual modalities. In the normal group of 5 subjects, 4 were tested with the auditory task and 2 with the visual task

and only the results from the auditory task were analysed. In the auditory task a sequence of two tones, 1.5 and 2.0 kHz in frequency, 50 ms in duration with rise and fall times of 10 ms, an intensity of between 50 and 70 dB nHL and an interstimulus interval of 1.2 s, were presented through earphones. The intensity level used was selected by the subject as being comfortable. The probability of the tone being higher pitched was 0.15. The subject was to press a response button when the higher pitched tone occurred. Separate averages to the rare and frequent auditory signals were made. Twenty-five trials to the higher pitched tone uncontaminated by eye movements were collected and a duplicate set of trials run again. In the visual task the two stimuli were an infrequent 'X' (probability 0.15) and a frequent 'T'. The subject was to press the response button every time the 'X' appeared. The visual stimuli were presented on a display placed 1.5 m in front of the subject with each letter subtending a visual angle of 12 min horizontally and 15 min vertically. The number of trials collected and their separation into rare and frequent categories was the same as in the auditory protocol. Reaction times for both modalities could be identified for up to 840 ms after stimulus presentation. A response to a stimulus occurring after that period could not be distinguished from the absence of response.

*Detection of a probe digit, the 'Sternberg' tasks (test b).* The experimental paradigm employed closely paralleled that described by Sternberg (1966) to evaluate short-term memory. Digits (1 to 9) were presented in strings of one or three items (in Case 1 a two-item string was also used). The time separation between each item in the string was 1.2 s. A 3 s pause followed the last item of the string before a test item, the probe, occurred (fig. 1). The probability that the probe was a member of the preceding string was 0.5. The subjects were instructed to press a response button if they identified the probe item as a member of the preceding string. If the probe was not in the preceding string the button was not to be pressed. The occurrence of a response (button press) was defined for each probe presentation along with its latency (reaction time). Event-related potentials were subsequently classified as being associated with a correct response (hit), a correct absence of response (correct rejection), a failure to respond (miss) or a response to a probe digit not occurring in the preceding set (false alarm). Five seconds elapsed after the presentation of the probe before the next trial commenced signalled by the word 'start' followed 0.85 s later by the items in the string. In contrast to the 'oddball' paradigm, the occurrence of a button press in this task could be defined for 4150 ms after the presentation of the probe, allowing event-related potentials to the probes to be accurately classified along with their associated reaction times. The digits contained in each trial were selected in a pseudorandom manner with the restriction that no probe digit could occur in two consecutive trials and no more than three consecutive correct or incorrect probes occurred in sequence. The proportion of correct probes relative to the position of the matching digit in the preceding string (i.e., first, second or third) was adjusted to be approximately equal.

The digits were presented in either of two ways in separate runs of the experiment. One was visually on a vide screen located 2 m in front of the subject with each digit subtending a visual angle of 12 min horizontally by 15 min vertically. The raster display of the vide screen produced a variable delay of up to 20 ms between the signal to start the display and the actual appearance of the digit. No effort was made to correct for this variability in the subsequent analysis of the event-related potentials. The second presentation mode was acoustic. The phonemic sequences comprising each digit and the word 'start' were generated by a personal computer (BBC model B fitted with a speech synthesizer) and presented by earphones at an intensity between 40 and 60 dB nHL, depending on each subject's assessment of what was 'comfortable and clear'. The onset of the earphone voltages occurred within 20 ms of the signal to initiate speech production. Both the test items and the probe were presented in the same modality except on one testing session for Case 1 when the modality of the test string and the probe could differ.

### *Procedure*

The subjects were presented with a series of practice trials using the digit probe identification task in the visual modality to acquaint them with the procedures and to instruct them how to relax their

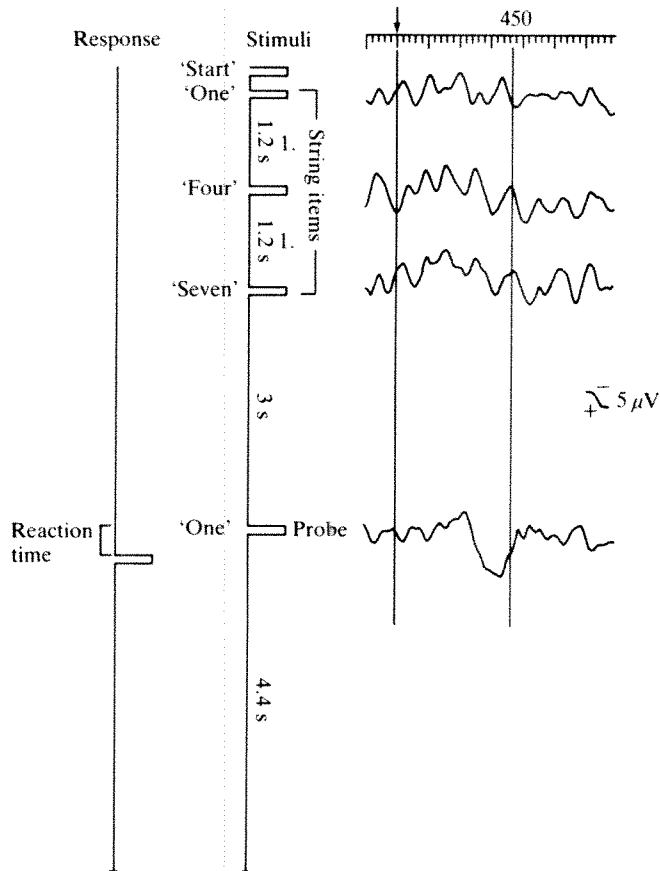


FIG. 1. Stimulus sequence employed in the probe identification tasks. The 'Stimuli' line contains pulses indicating the initiation of the trial ('Start') followed by the string items to be remembered and the probe to be identified. The temporal relationship between the items is noted in seconds (s) between the pulses. The stimuli could be presented acoustically or as arabic symbols in the visual modality. The occurrence of the button press to the probe is indicated in the line labelled 'Response' and its latency as 'Reaction time.' Examples of the EEG of individual trials (recorded between Pz and linked earlobes) accompanying both the string items and the probe are to the right of the figure. The time difference between the large vertical marks on the time base is 120 ms. The arrow at the initial vertical line marks the stimulus onset and the second vertical line marks the 450 ms poststimulus time. Note the appearance of a large positive deflection in the potential evoked by the probe at approximately 400 ms.

facial muscles and reduce the frequency of blinking. Data collection began with the digit sequences being presented in blocks of 20 trials beginning with the one-item test string in the visual modality and alternating in a balanced design with the auditory mode. The three-item sequences followed after four blocks of the single item string had been presented and then the one and three-item test sequences alternated until at least 20 trials containing a correctly identified in-set probe (hits) for the single item sequences and 40 trials for the three-item sequences in each modality had been collected. In one of the patients (Case 1) we also presented test strings containing two items. At the end of the probe detection tasks the subjects were tested with the infrequent stimulus detection tasks, i.e., the 'oddball' paradigms.



### *Data Analysis*

The event-related potentials for each trial were stored in digital form on magnetic tape. These single trials were sorted according to response type and then combined to make group averages for 'hits', 'misses', etc. Averages were filtered with a zero phase shift low band pass digital filter having a cut-off at 30 Hz for display and measurement. The amplitudes and latencies of the peaks of the components were measured at those electrode sites where they were most prominent (*see* figs 2 and 3 for examples of the wave forms). Amplitude was defined as the difference between the mean of the baseline voltage in the 120 ms preceding stimulus presentation and the voltage at the peak of the component. In the auditory 'oddball' tasks there was a sequence of components designated as N100 (largest at Fz or Cz), P200, N250 and P300 (all largest at Cz or Pz). In the visual tasks the sequence was similar except that the N100 could not be identified consistently. In the digit identification tasks in the auditory modality the earliest consistent peak occurred at about 150 ms, was of negative polarity (N150) and was of largest amplitude frontally. In the visual modality the earliest consistent peak also occurred at approximately 150 ms but was of positive polarity (P150) and most prominent frontally or centrally. In both modalities a negativity occurred in response to the probe at approximately 200 to 300 ms that was largest centrally and parietally. This component (N250) was occasionally separated from the N150 component by a brief positive-going deflection. However, in many averages to the auditory probe the trace remained negative after the N150 with several smaller negative deflections superimposed until it turned positive to form the next component. This turning point was selected as the latency of N250. Its amplitude was often slightly positive relative to the prestimulus baseline. The subsequent large positive deflection (P450) was long-lasting and did not return to baseline before the end of the analysis window (960 or 1280 ms). We chose to measure amplitude at the peak of this deflection at the midline parietal electrode (Pz). This was done by drawing lines paralleling the positive-going slope and the sustained positive shift and choosing the latency at their point of intersection. An earlier deflection (P350) was most prominent frontally (Fz) but this component was not measured because it could not be identified consistently in every subject in the control population.

Latency and amplitude measures were made on the averages evoked by the probes classified as hits, correct rejections, misses or false alarms. A second set of analyses was performed separating the single trials comprising the correctly identified probes (hits) into new averages formed as a function of the associated reaction times, i.e., the fastest third, the middle third and the slowest third. A third set of analyses was performed on the event-related potentials associated with correctly identified probes (hits) as a function of the position of the matching digit in the preceding string, that is, first, second or third item.

Reaction times and P450 latencies and amplitudes were analysed using repeated measures analysis of variance (ANOVA) with program BMDP2V of the Biomedical Computing Package (Dixon, 1983). Although an unweighted means solution may be more appropriate for comparing groups of unequal size in repeated measures designs, the least squares ANOVA provided by program BMDP2V produces a similar result when the group sizes are not markedly different, as is the case here (Winer, 1971). Probability values for significant within group factors reported in this paper are those obtained using the Greenhouse-Geisser correction available in program BMDP2V.

## RESULTS

### *Performance*

Performance was relatively free of errors on digit probe identification for normal subjects with the exception of an occasional response to a probe not contained in the preceding test string (false alarm). In contrast, the patients had varying degrees of difficulty on these tasks (Table 2). Case 1, tested on three occasions over three

TABLE 2. PERFORMANCE ON THE DIGIT IDENTIFICATION TASKS

| Modality        | <i>Auditory</i> |     |          |     | <i>Visual</i> |     |          |     |
|-----------------|-----------------|-----|----------|-----|---------------|-----|----------|-----|
|                 | <i>1</i>        |     | <i>3</i> |     | <i>1</i>      |     | <i>3</i> |     |
| String length   |                 |     |          |     |               |     |          |     |
| Probe response  | %Hits           | %FA | %Hits    | %FA | %Hits         | %FA | %Hits    | %FA |
| <b>Patients</b> |                 |     |          |     |               |     |          |     |
| 1, a            | 100             | 0   | 62       | 11  | 100           | 0   | 96       | 4   |
| b               | 100             | 0*  | 81       | 15  | 100           | 0*  | 100      | 0   |
| 2               | 100             | 0   | 84       | 4   | 100           | 0   | 85       | 1   |
| 3, a            | 100             | 0   | 77       | 0   | 100           | 0   | 92       | 0   |
| b               | 100             | 0   | 100      | 0   | 100           | 0   | 96       | 0   |
| 4               | 77              | 7   | 63       | 8   | 87            | 2   | 60       | 0   |
| Normals         | 100             | <1  | 100      | 1   | 100           | <1  | 100      | 3   |

Hits=correct responses to in-set probes. FA=false alarms; incorrect responses to out-of-set probes. The number of trials contributing to these measures ranged from 29 to 81. \*String length of 2 in the auditory modality: Hits=90%, FA=10%; String length of 2 in the visual modality: Hits=98%, FA=0%. a and b refer respectively, to the initial and subsequent evaluations.

weeks (two of which are in Table 2 and the other is in Table 4) had a stable and substantial deficit on the three-item auditory task. With a two-item auditory string the deficit was much less. Case 2 showed a slight impairment in performance in both modalities to strings containing three items. Case 3 had a greater impairment on the three-item string during auditory (77% accuracy) compared to visual presentation (92% accuracy) on the initial testing session (test a). The improvement in performance to 100% for the auditory modality and to 96% for the visual modality on the second test (test b) coincided with the improvement in his clinical condition. Case 4 did not perform much above chance in either modality when the number of items in the string was three and even missed a number of matching probes when only one item was presented. This latter patient was the only subject whose performance on detecting the rare stimulus in the 'oddball' task was impaired as judged by the absence of a button press within 840 ms of the presentation of the target on one-third of the trials and by a false alarm rate of approximately 10%.

Further data analysis is described first in terms of overall performance using reaction times and event-related potential wave forms obtained from all accepted trials and secondly, in terms of data obtained by selectively averaging potentials according to reaction time or to the position of the matching stimulus in the presentation set.

### *Reaction Times*

Mean reaction times and SDs are given in Table 3 and significant comparisons from the repeated measures ANOVA for the digit identification task appear in Table 6. These analyses include only the initial testing session for the first 3 cases and exclude Case 4 whose performance on the three-item string was at chance and both impaired and slowed on the one-item string. The patients' reaction times were

TABLE 3. REACTION TIMES IN MS TO THE PROBES ON THE DIGIT IDENTIFICATION AND TO THE TARGETS ON THE RARE SIGNAL DETECTION TASKS (MEAN (SD))

| Modality         | Auditory  |           |          | Visual    |           |          |            |            |
|------------------|-----------|-----------|----------|-----------|-----------|----------|------------|------------|
| Test             | 1-item    | 3-item    | Rare     | 1-item    | 3-item    | Rare     | Aud<br>3-1 | Vis<br>3-1 |
| <b>Patients</b>  |           |           |          |           |           |          |            |            |
| 1, a*            | 609(129)  | 915(304)  | 578(118) | 477(58)   | 607(123)  | 562(142) | 306        | 130        |
| b**              | 561(123)  | 811(223)  | 393(76)  | 477(78)   | 614(120)  | NT       | 250        | 147        |
| 2*               | 629(108)  | 862(293)  | 426(120) | 554(116)  | 710(277)  | 446(72)  | 233        | 156        |
| 3, a*            | 664(96)   | 1121(559) | 414(93)  | 756(264)  | 779(311)  | 433(50)  | 457        | 23         |
| b                | 740(80)   | 883(179)  | NT       | 738(74)   | 770(136)  | NT       | 143        | 32         |
| 4                | 1285(516) | 1338(519) | ?        | 1224(224) | 1348(469) | ?        | 53         | 124        |
| $\bar{X}$ of*    | 634(28)   | 966(137)  | 473(91)  | 596(144)  | 699(87)   | 480(71)  | 332        | 103        |
| $\bar{X}$ of SD* | 111(17)   | 385(150)  | 110(15)  | 146(106)  | 237(10)   | 88(48)   | 274        | 71         |
| <b>Normals</b>   |           |           |          |           |           |          |            |            |
| Male, 53 yrs     | 450(87)   | 488(95)   | 332(52)  | 403(72)   | 457(85)   | 371(56)  | 38         | 54         |
| Male, 55 yrs     | 306(49)   | 437(75)   | 250(30)  | 323(49)   | 407(75)   | 386(62)  | 131        | 83         |
| Male, 57 yrs     | 564(83)   | 564(70)   | 296(45)  | 520(90)   | 579(123)  | NT       | 0          | 59         |
| Female, 40 yrs   | 478(98)   | 582(80)   | NT       | 529(68)   | 576(120)  | NT       | 104        | 47         |
| Female, 53 yrs   | 569(80)   | 672(88)   | 498(74)  | 517(90)   | 585(80)   | NT       | 103        | 68         |
| $\bar{X}$        | 473(107)  | 549(90)   | 344(108) | 458(92)   | 521(83)   |          | 76         | 63         |
| $\bar{X}$ of SD* | 76(18)    | 82(10)    | 50(18)   | 77(18)    | 97(23)    |          | 6          | 20         |

\* Indicates the first testing session for the patients included in the mean ( $\bar{X}$  of \*) and mean ( $\bar{X}$  of SD\*). \*\* String length of 2 in the auditory modality: 733(285). String length of 2 in the visual modality: 594(105). NT = not tested. ? = values could not be derived due to slowed or absent responses. a and b refer, respectively, to the initial and subsequent evaluations.

significantly longer than those of the normal controls (g term in Table 6), especially for the auditory modality (sg term) and the three-item presentation set (ig term). The difference between the auditory reaction times in the three and one-item conditions compared with the visual reaction times in the same conditions was significantly greater for patients than controls (332 vs 76 ms for auditory, 103 vs 63 ms for visual; sig term in Table 6). Note from Table 3 the similarity of the reaction times between the two tests (a and b) in Case 1, a patient with stable clinical deficits and the shortening of the reaction times in Case 3, a patient whose deficits of digit span and word repetition improved in the period between the two tests.

As well as differences in absolute reaction times between patients and normal controls, the patients also showed considerably more variability (see SD columns in Table 3). This heightened variability is particularly prominent both with auditory strings of three items (mean of 82 ms in normals vs 385 ms in patients) and with the increase in auditory string length from one to three items (3-1 difference of 6 ms in normals vs 274 ms for patients).

Case 1 was tested with two-item strings in both the auditory and visual modalities. There was a substantial increase in both the mean reaction times (172 and 117 ms,

respectively) and their SDs (162 and 27 ms, respectively) compared with these measures to the one-item strings. Thus in this patient, both accuracy and reaction time became impaired when the number of items to be remembered exceeded the patient's digit span as defined by repetition of orally presented items.

The reaction times to the detection of the rare event in the auditory 'oddball' task were approximately 150 ms faster than those to the identification of the correct probe (hits) on the one-item auditory string in the Sternberg paradigm for both the patient and normal groups (Table 3). The increased variability of reaction times in the patients compared with normals is evident even in the 'oddball' task.

#### *Performance and Reaction Time on Crossed Modal Digit Probe Identification*

In Case 1 we had the opportunity to assess whether the deficits in accuracy and reaction time on the identification of the probe in the Sternberg tasks of auditory short-term memory were affected by presenting the items to be remembered in one modality and using a probe of the opposite modality. For example, could the poor performance with auditory presentation of both items to be remembered and the probe be improved by changing the probe presentation to the visual modality? Presenting the three-item string in the auditory modality and testing with a visual probe barely affected accuracy or reaction time (aud/aud vs aud/vis for three-item string in Table 4). In contrast, the mean reaction time lengthened by approximately 300 ms and its SD increased three-fold when a visually presented string was probed in the auditory mode (vis/vis vs vis/aud for three-item string in Table 4). Introducing an auditory component even with a one-item string impaired accuracy and slowed reaction time.

All these results document the impairment of short-term memory in these patients particularly when the auditory modality is employed. The main deficit is in ident-

TABLE 4. PERFORMANCE AND REACTION TIMES IN MS ON CROSS-MODAL DIGIT IDENTIFICATION TASKS IN CASE 1 (STRING MODALITY/PROBE MODALITY)

|                         | <i>Performance</i> |             | <i>Reaction time</i> |
|-------------------------|--------------------|-------------|----------------------|
|                         | <i>% Hits</i>      | <i>% FA</i> | <i>Mean (SD)</i>     |
| String length of 1 item |                    |             |                      |
| Aud/aud*                | 100                | 0           | 561(129)             |
| Aud/vis                 | 100                | 10          | 706(331)             |
| Vis/vis*                | 100                | 0           | 477(78)              |
| Vis/aud                 | 93                 | 0           | 712(142)             |
| String length of 3      |                    |             |                      |
| Aud/aud                 | 73                 | 12          | 887(279)             |
| Aud/vis                 | 73                 | 27          | 859(277)             |
| Vis/vis                 | 95                 | 5           | 630(90)              |
| Vis/aud                 | 90                 | 3           | 975(290)             |

Aud and vis = auditory and visual, respectively. Hits = correct responses to in-set probes. FA = false alarms; incorrect responses to out-of-set probes. \* Values derived from test b of Table 2.

ifying probes when the number of items to be remembered increases from one to three digits. Even when the patients were correct in identifying matching probes their reaction times increased excessively and were more variable than for the shorter string length. Evaluation of the event-related potentials accompanying the presentation of the probes and the patients' responses may clarify some of the neural processes underlying this deficit of auditory short-term memory.

#### *Event-related Potentials: Scalp Distribution*

The scalp distribution of the averaged potentials from 1 normal subject to the correctly identified matching digits in the three-item auditory and visual probe identification tasks is illustrated in fig. 2. The components are labelled with P or N reflecting their polarity and a number indicating their approximate latency in ms. Note the presence of an early frontal component that is negative for the auditory modality (N150) and positive for the visual mode (P150). For the auditory modality there is an extension of the N150 negativity to form an N250 component, whereas for the visual modality the P150 is succeeded by an N250 component. In both modalities there follows a sustained high amplitude positive deflection that is widespread but largest over the parietal region. The positivity could be subdivided into an earlier P350 component prominent frontally and a parietal P450 component. The potentials in the probe identification tasks differ from the event-related potentials recorded to the detection of the infrequent stimulus in the 'oddball' task (fig. 2) by the absence of a P200 component, the long duration of the late positive deflection (the P450 component compared to the P300 component in the 'oddball' task) and the longer latency of all components.

#### *Event-related Potentials to the Probes in the Digit identification Tasks as a Function of the Number of Items in the Presentation Set*

Event-related potentials recorded at Pz for hits and correct rejections obtained from all normal subjects and patients for the one and three-item strings are shown in fig. 3. The normal subjects' traces are shown for hits on the three-item task on the right side of the figure (Normal Hit<sub>3</sub>) along with the grand average. There is a striking disparity between the amplitudes of the P450 component evoked during the auditory tasks in the normal and patient groups with the latter being quite small. In contrast, the potentials to the visual tasks are comparable in the two groups. Note that in both modalities the P450 components associated with correct rejections (CR in fig. 3) are of large amplitude and similar in morphology to the P450 component associated with hits. Thus probes evoked comparable P450 components regardless of their relation to the items in the preceding set, a feature which is in direct contrast to the small-to-absent P300 component evoked by the frequent stimulus in the 'oddball' tasks.

Measures of the amplitude and latency of the components evoked by the probe stimuli in the Sternberg task and by the infrequent stimuli in the 'oddball' task are contained in Table 5. The major differences between the patients and the normal

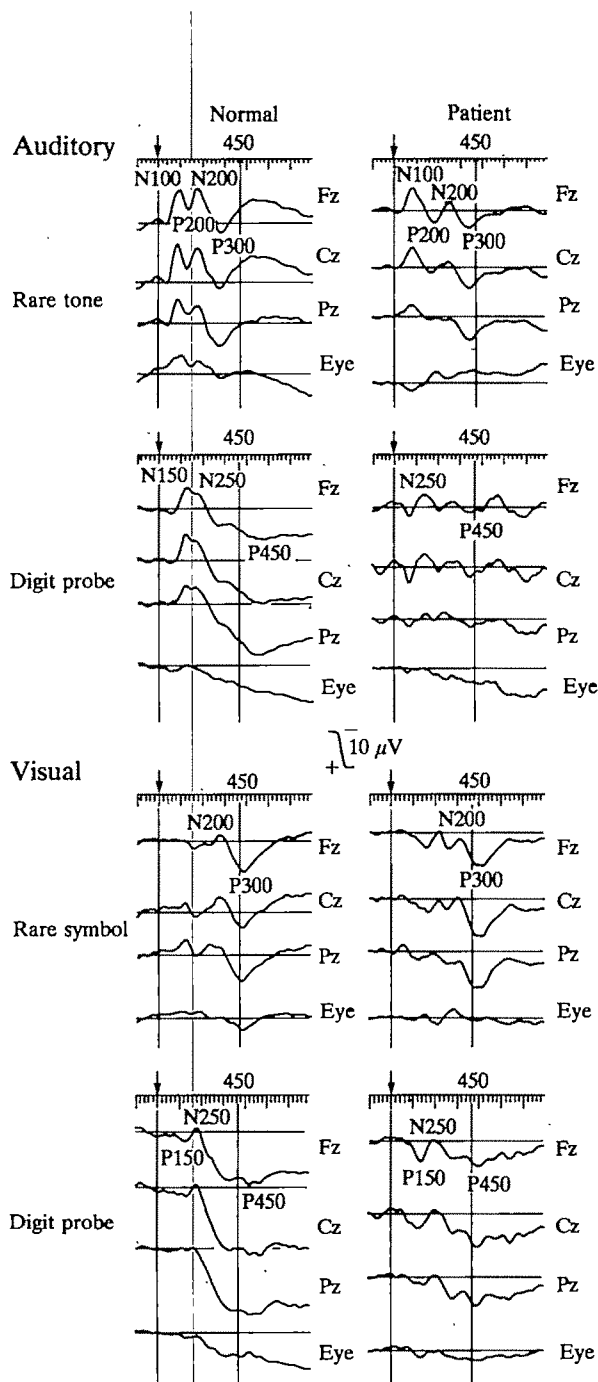


FIG. 2. Scalp distribution of the potentials at Fz, Cz and Pz referenced to linked earlobes along with the monitor of eye movements ('Eye') evoked by the stimuli in the two tasks used in this study that were accompanied by a correct response. The first task required the detection of a rare signal (a tone in the auditory modality and a symbol in the visual modality) occurring with a probability of 0.15 in a train of frequent stimuli and the second task required the identification of a probe as having been a member of a preceding set of items (see fig. 1 for a representation of this second task). The event-related potentials shown are from a normal subject (male, aged 55 yrs) and one of the patients with impaired auditory short-term memory (Case 1, test a). The components are labelled by their polarity (P or N for positive or negative) and their approximate latency in ms. Note that the event-related potentials to the rare stimuli are fairly similar in the normal subject and patient. In contrast, the event-related potentials to the digit probes show that the amplitude of a positive deflection at approximately 450 ms in the auditory digit probe task is difficult to define in the patient compared with the normal subject and is present but small relative to the normal subject for the visual digit probe. In this and all subsequent figures, the initial vertical line in the averages marked by an arrow indicates the occurrence of the stimulus. The distance between the large vertical deflections on the time base is 120 ms.

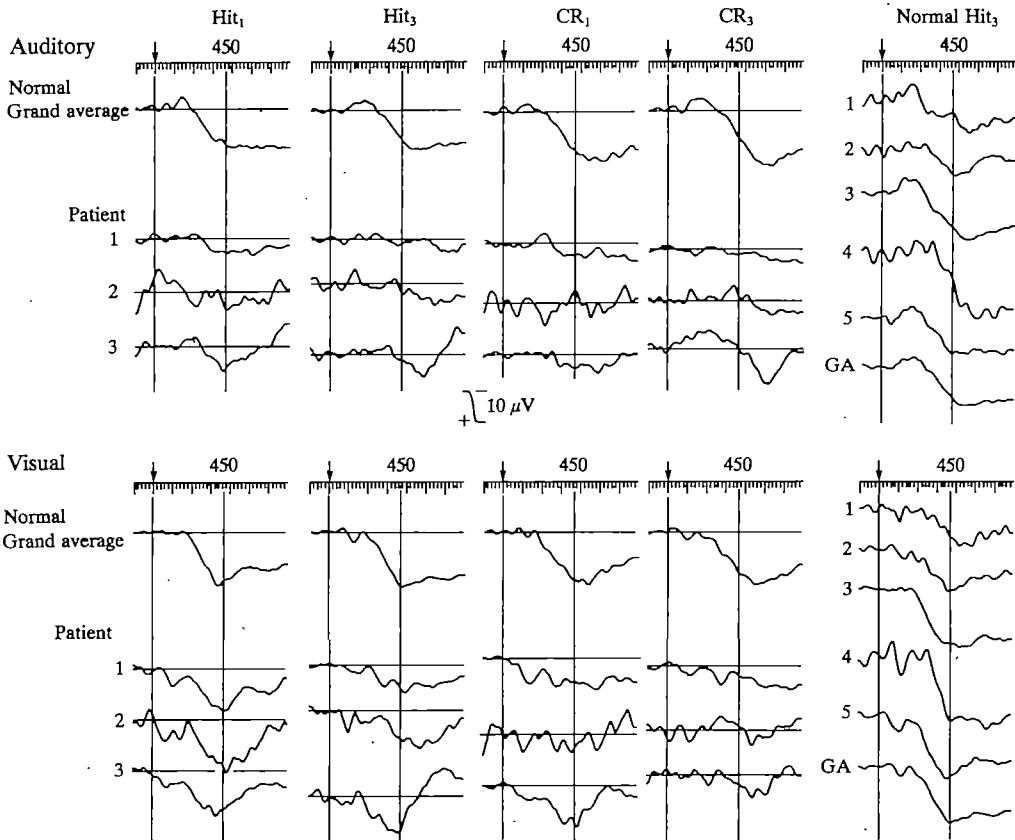


FIG. 3. Event-related potentials (Pz referenced to linked earlobes) accompanying the presentation of the probe following one or three-item strings with auditory and visual presentations. The panels on the right labelled 'Normal Hit<sub>3</sub>' contain the event-related potentials from the 5 normal controls and their grand average (GA) to in-set probes that were associated with a correct button response following the presentation of three-item strings (Hit<sub>3</sub>). The grand average of the normals as a function of the number of items in the string (1 or 3) and the response category (Hits, Correct Rejections labelled 'CR') is shown with the 3 patients' event-related potentials in the other portions of the figure.

subjects are in the P450 component. Significant comparisons from the repeated measures ANOVA of P450 latency and amplitude for hits and correct rejections in the digit probe identification task appear in Table 6. P450 amplitudes were significantly smaller for patients (g term in Table 6). They were also smaller for auditory stimuli (s term) with this effect being significantly more pronounced in the patient group (sg term). P450 latency was longer for auditory than visual stimuli (s term) as were the latencies to the three-item set compared with the single item set (i term). This latter effect was significantly more pronounced for auditory than visual stimuli (si term). P450 latency for correct rejections was significantly longer than for hits (c term).

TABLE 5. LATENCY IN MS AND AMPLITUDE IN  $\mu$ V OF EVENT-RELATED POTENTIALS

| TASK     |           |                        |            |                        |            |                       |            |                       |            |                       |            |
|----------|-----------|------------------------|------------|------------------------|------------|-----------------------|------------|-----------------------|------------|-----------------------|------------|
| Category |           | <i>Hit<sub>1</sub></i> |            | <i>Digit probe</i>     |            |                       |            |                       |            | <i>'Oddball' Rare</i> |            |
|          |           |                        |            | <i>Hit<sub>2</sub></i> |            | <i>CR<sub>1</sub></i> |            | <i>CR<sub>2</sub></i> |            |                       |            |
|          |           | <i>Lat</i>             | <i>Amp</i> | <i>Lat</i>             | <i>Amp</i> | <i>Lat</i>            | <i>Amp</i> | <i>Lat</i>            | <i>Amp</i> | <i>Lat</i>            | <i>Amp</i> |
| Auditory |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| N150     |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| Patient  | $\bar{X}$ | 164                    | 3.8        | 175                    | 3.8        | 170                   | 2.5        | 169                   | 4.2        | 108                   | 4.4        |
|          | SD        | 33                     | 1.3        | 31                     | 3.0        | 37                    | 1.0        | 22                    | 1.0        | 10                    | 3.2        |
| Normal   | $\bar{X}$ | 155                    | 5.3        | 171                    | 4.9        | 154                   | 5.2        | 160                   | 5.3        | 93                    | 7.2        |
|          | SD        | 13                     | 1.7        | 18                     | 1.6        | 20                    | 2.7        | 15                    | 1.7        | 11                    | 1.7        |
| P200     |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| Patient  | $\bar{X}$ | ----- ND -----         |            |                        |            |                       |            |                       |            | 191                   | 3.8        |
|          | SD        |                        |            |                        |            |                       |            |                       |            | 21                    | 2.4        |
| Normal   | $\bar{X}$ | ----- ND -----         |            |                        |            |                       |            |                       |            | 170                   | 5.6        |
|          | SD        |                        |            |                        |            |                       |            |                       |            | 12                    | 3.3        |
| N250*    |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| Patient  | $\bar{X}$ | 295                    | 2.0        | 348                    | 2.2        | 324                   | 3.2        | 383                   | 3.9        | 268                   | +1.3       |
|          | SD        | 83                     | 1.0        | 66                     | 0.5        | 97                    | 0.2        | 125                   | 3.0        | 37                    | 2.0        |
| Normal   | $\bar{X}$ | 233                    | 1.3        | 235                    | 4.2        | 247                   | 1.1        | 225                   | 2.4        | 221                   | 0.6        |
|          | SD        | 25                     | 1.3        | 56                     | 1.2        | 34                    | 1.7        | 80                    | 3.1        | 16                    | 2.9        |
| P450     |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| Patient  | $\bar{X}$ | 441                    | 5.7        | 642                    | 5.6        | 438                   | 4.3        | 646                   | 6.6        | 387                   | 9.9        |
|          | SD        | 19                     | 1.9        | 62                     | 1.6        | 95                    | 0.9        | 46                    | 3.9        | 34                    | 4.1        |
| Normal   | $\bar{X}$ | 455                    | 14.6       | 519                    | 13.6       | 488                   | 14.9       | 602                   | 16.9       | 343                   | 13.1       |
|          | SD        | 91                     | 2.2        | 66                     | 5.2        | 83                    | 5.3        | 35                    | 7.0        | 18                    | 7.8        |
| Visual   |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| P150     |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| Patient  | $\bar{X}$ | 147                    | 5.2        | 143                    | 4.0        | 158                   | 4.8        | 134                   | 3.3        | ND                    |            |
|          | SD        | 23                     | 2.2        | 21                     | 1.6        | 26                    | 2.3        | 20                    | 1.7        |                       |            |
| Normal   | $\bar{X}$ | 141                    | 2.8        | 150                    | 3.5        | 127                   | 3.2        | 152                   | 4.4        | **                    |            |
|          | SD        | 14                     | 1.3        | 34                     | 0.7        | 59                    | 2.4        | 33                    | 2.0        |                       |            |
| N250     |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| Patient  | $\bar{X}$ | 219                    | +2.3       | 250                    | 0.0        | 255                   | +0.4       | 294                   | 1.7        | 301                   | +1.5       |
|          | SD        | 22                     | 1.2        | 72                     | 1.5        | 16                    | 3.8        | 51                    | 1.8        | 66                    | 3.2        |
| Normal   | $\bar{X}$ | 213                    | 0.9        | 231                    | 1.7        | 224                   | 0.3        | 278                   | 0.2        | **                    |            |
|          | SD        | 36                     | 2.4        | 38                     | 4.4        | 65                    | 2.5        | 56                    | 3.4        |                       |            |
| P450     |           |                        |            |                        |            |                       |            |                       |            |                       |            |
| Patient  | $\bar{X}$ | 436                    | 14.8       | 476                    | 10.2       | 545                   | 10.1       | 558                   | 6.5        | 441                   | 16.6       |
|          | SD        | 31                     | 1.8        | 71                     | 1.5        | 74                    | 3.1        | 53                    | 1.1        | 25                    | 7.0        |
| Normal   | $\bar{X}$ | 424                    | 18.0       | 450                    | 17.2       | 469                   | 15.6       | 535                   | 16.8       | **                    |            |
|          | SD        | 51                     | 3.5        | 31                     | 3.7        | 68                    | 6.4        | 38                    | 4.2        |                       |            |

\* 4 of the 5 normals were tested. \*\* 2 of the 5 normals were tested but data not included. CR = correct rejections. ND = not detected. Lat = latency. Amp = amplitude.



TABLE 6. SIGNIFICANT COMPARISONS FROM REPEATED MEASURES ANOVA OF OVERALL REACTION TIMES AND GRAND AVERAGE P450 LATENCIES AND AMPLITUDES IN THE DIGIT PROBE IDENTIFICATION TASK

|                | <i>ANOVA term</i> | <i>P</i> |
|----------------|-------------------|----------|
| Reaction time  | g                 | *        |
|                | s                 | **       |
|                | sg                | **       |
|                | i                 | ***      |
|                | ig                | ***      |
|                | si                | *        |
|                | sig               | *        |
| P450 latency   | s                 | *        |
|                | i                 | ***      |
|                | si                | *        |
|                | c                 | **       |
| P450 amplitude | g                 | *        |
|                | s                 | ***      |
|                | sg                | **       |
|                | ig                | *        |
|                | sc                | *        |

ANOVA terms: g=subject group (control or patient); s=stimulus modality (auditory or visual); i=number of items in presentation set (1 or 3); c=response category (hit or correct rejection). \*\*\*  $P < 0.001$ , \*\*  $P < 0.01$ , \*  $P < 0.05$ .

### *Event-related Potentials to the Probes in the Digit Identification Tasks as a Function of Reaction Time*

The finding from the analysis of the overall data that P450 amplitudes are reduced on those tasks of auditory short-term memory for which the patients' performance was also impaired (percentage accuracy and reaction times) are congruent. However, the observation that P450 amplitudes were similar in both the one-item task of auditory short-term memory, when the patients performed almost like normals, and the three-item task, when their performance was grossly impaired, was unexpected and merited further inspection. We therefore examined the potentials associated with hits as a function of reaction time for each subject (fastest third, middle third, slowest third) as well as with the serial position of the matching stimulus in the three-item task (first, second or third).

Fig. 4 contains the event-related potentials from both a normal subject and a patient for hit trials analysed according to reaction time. In the patient, there is a remarkable increase in P450 amplitude in the one-item auditory task for those probes associated with the fastest reaction times, whereas the changes are minimal for the three-item auditory task and for both visual tasks. It is particularly apparent in the one-item auditory task that the P450 component, which is difficult to define

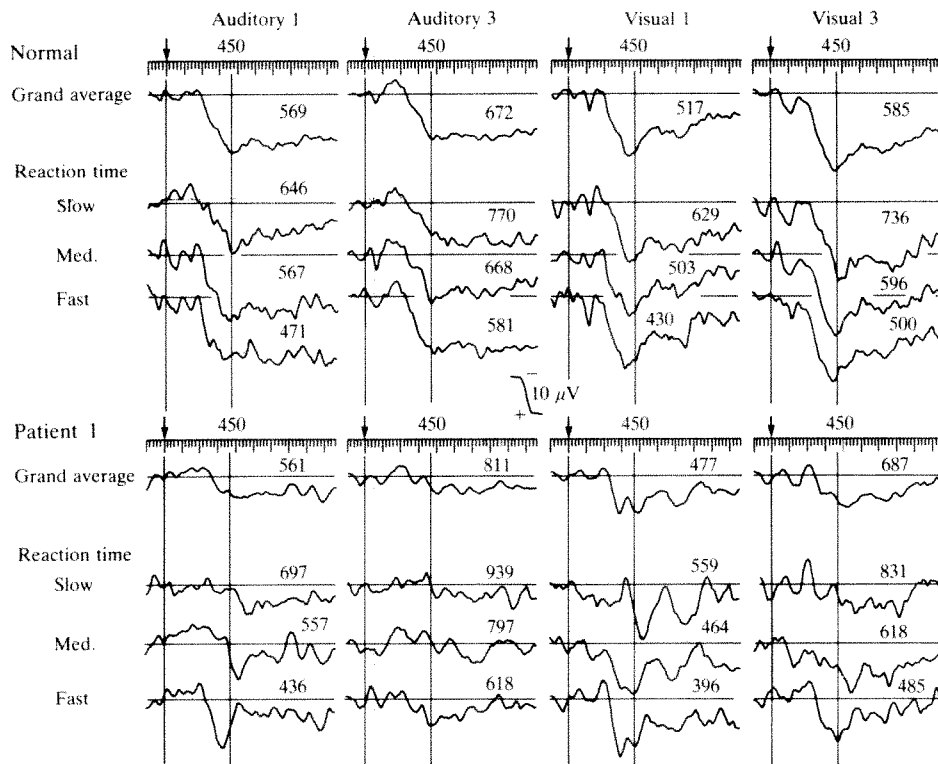


FIG. 4. Effect of averaging event-related potentials to correctly identified in-set probes as a function of reaction times. The trials comprising the grand average were subdivided approximately into thirds according to reaction time: fastest third ('Fast'), medium third ('Med.'), and slowest third ('Slow'). The event-related potentials from a control subject (female, aged 53 yrs, the wife of Case 1) and from Case 1 on the second testing session (test b) are presented in both the visual and auditory modalities. The numbers above each average represent the mean reaction time for the trials comprising that particular average. Note the profound effect that reaction time speeds have on the latency of the initial portion of the positive component occurring at about 450 ms in the patient in both modalities compared with the normal subject. The amplitude of this positive deflection in the patient is enhanced as a function of reaction time only following the one-item string in the auditory modality. The time base in this figure is 1280 ms compared with the 960 ms employed in the other figures.

in the grand average, becomes clear as the average is subdivided according to reaction time. This increase in amplitude of the P450 component is transient, principally involving the earliest portion of the component without affecting the sustained portion of the deflection. There are only slight changes in amplitude of the normal subject's P450 components as a function of reaction time.

Fig. 5 compares mean values of reaction times and P450 latencies and amplitudes for the patients and normal control groups according to stimulus modality (auditory and visual) to the correctly identified probes (hits). Table 7 contains the significant comparisons from the repeated measures ANOVA of the data summarized in fig. 5. The mean data for the auditory P450 amplitude associated with fast reaction times confirm the observation from the single patient depicted in fig. 4 that for the single-item set this amplitude is equivalent to that for normal controls.

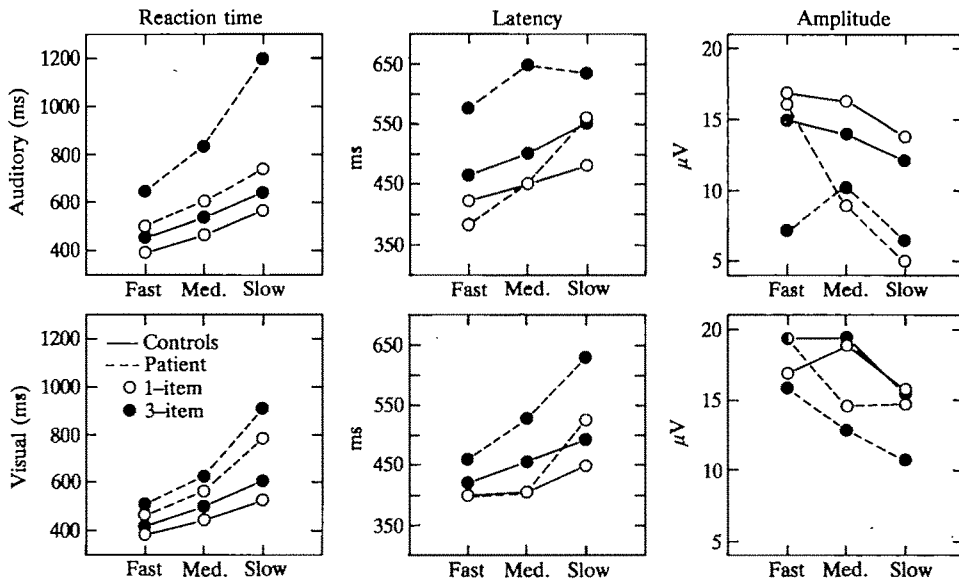


FIG 5. Comparison of mean reaction times and P450 latencies and amplitudes for hit trials in the digit probe identification task averaged according to fast, medium or slow reaction time in the auditory and visual modalities. The ANOVA analyses of these data are given in Table 7. Open circles are from the one-item presentation set and filled circles from the three-item presentation set. Data from controls are indicated by solid lines, and those from patients by interrupted lines.

This observation contrasts sharply with that for the grand average data in which there is a difference of 8.9  $\mu V$  between controls and patients for the P450 component accompanying the probe in the single-item task. The increase in P450 latency from the one to three-item presentation sets was significantly greater for patients than controls (ig term in Table 7), paralleling a similar increase in reaction time. P450 latency increased and P450 amplitude decreased with increasing reaction time (r term). The general conclusion to be drawn from fig. 5 and Table 7 is that the patients' performance and event-related potential measures are comparatively similar to those for controls for fast reaction times in the one-item task but that these parameters deteriorate dramatically for the three-item presentation set, particularly in the auditory modality.

With regard to individual patients, Case 1, whose neurological deficits were stationary, had similar enhancements of P450 amplitude for fast reaction time trials in the one-item auditory condition on both testing sessions. However, Case 3, who recovered between tests, showed a substantial enhancement of P450 amplitude at the first recording session and comparatively little change at the second test.

In contrast to the influence of reaction time on both the latency and amplitude of P450, the analysis of the event-related potentials to probes as a function of the position of the matching digit in the preceding set showed no apparent effects.

These results may provide an explanation for the finding in patients of a reduced

TABLE 7. SIGNIFICANT COMPARISONS FROM REPEATED MEASURES ANOVA OF REACTION TIMES AND P450 LATENCIES AND AMPLITUDES FOR DATA DIVIDED ACCORDING TO FAST, MEDIUM OR SLOW REACTION TIMES IN THE DIGIT PROBE IDENTIFICATION TASK

|                | <i>ANOVA term</i> | <i>P</i> |
|----------------|-------------------|----------|
| Reaction time  | g                 | *        |
|                | s                 | **       |
|                | sg                | *        |
|                | i                 | ***      |
|                | ig                | **       |
|                | si                | *        |
|                | sig               | *        |
|                | r                 | ***      |
|                | rg                | **       |
|                | ir                | ***      |
|                | irg               | ***      |
| P450 latency   | i                 | ***      |
|                | ig                | *        |
|                | r                 | ***      |
| P450 amplitude | g                 | *        |
|                | s                 | ***      |
|                | r                 | *        |

ANOVA terms are: g=subject group (control or patient); s=stimulus modality (auditory or visual); i=number of items in presentation set (1 or 3); r=reaction time division (fast, medium, slow). \*\*\*  $P < 0.001$ , \*\*  $P < 0.01$ , \*  $P < 0.05$ .

amplitude of P450 to hits in the one-item auditory memory task. The patients had an increase in the peak latency of P450 of 180 ms between the fastest and slowest reaction time divisions, whereas in the normal group the peak latency increased by only 60 ms. Thus in the process of averaging all of the single trials to form the grand average, the P450 component will show a loss of amplitude due to cancellation by overlapping of preceding N250 components from 'slow' reaction time trials with P450 components from 'fast' reaction time trials. This process of cancellation is prominent in the patients' averages and only slightly evident in the normals' averages. Superimposition of the single trials comprising the three reaction time divisions for a normal subject and a patient (fig. 6) shows how readily the average will be confounded in the latter but not the former. It is clear, therefore, that the patient group can form normal-sized P450 components in the one-item auditory task but their latency variability is an important factor accounting for the reduction of amplitude of the grand average of all single trials. The effect of selective averaging by latency of reaction time on the amplitude of P450 seems to enhance the earliest portions of the P450 component as the sustained portions of this deflection are barely affected. The reduction in amplitude of the P450 component evoked in the three-item auditory task could not be modified by selective averaging.

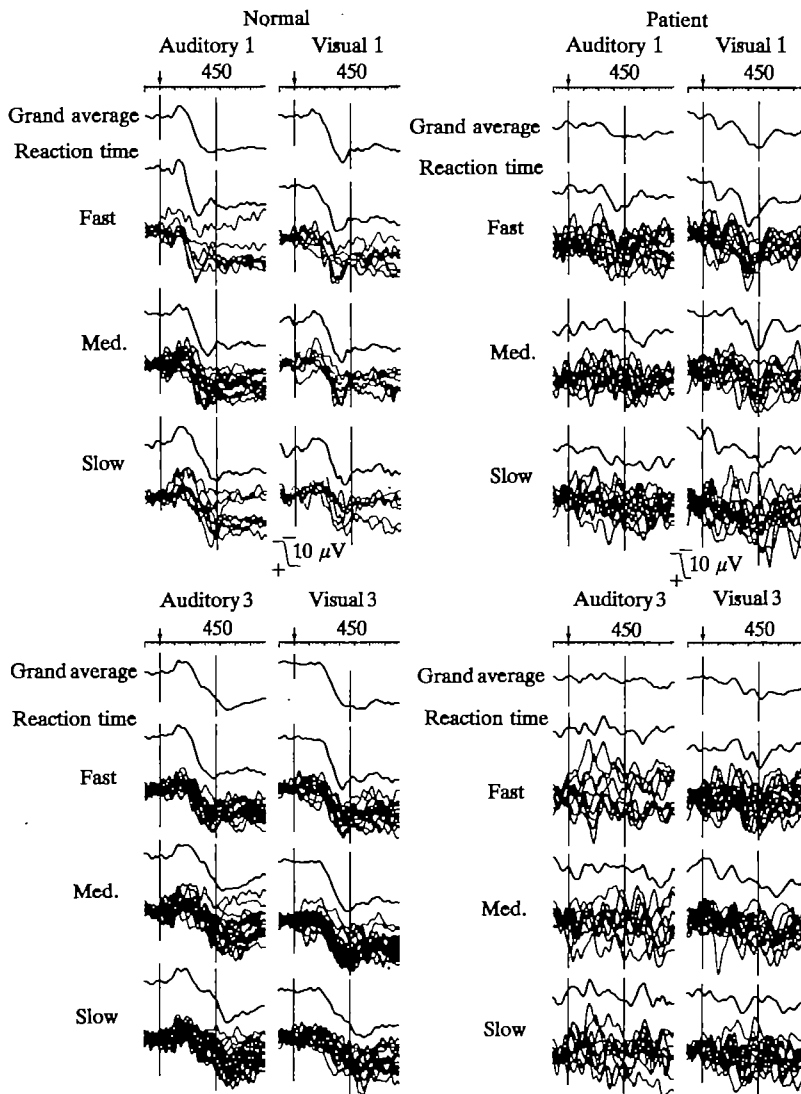


FIG. 6. This shows how the latency of individual event-related potentials in a patient can vary with reaction time and affect the grand average in comparison with a normal control subject. The individual trials evoked by the correctly identified in-set probe in the auditory and visual modalities were subdivided into three groups as a function of reaction time and then the average made of these subgroups. Note that the latency shift of the individual event-related potentials in the patient as a function of the reaction times (Fast, Med., Slow) results in major differences in amplitude and latency between the newly created averages and thus leads to attenuation of components in the grand average, particularly a reduction in amplitude of the P450 component. The latency shifts in a normal control (male, aged 57 yrs) are much less and therefore the grand average is little affected in amplitude.

## DISCUSSION

*Reaction Time Measures in the Digit Identification Tasks*

The results of this study in patients with disordered short-term memory show that measures of reaction time in a probe identification task can provide quantitative indices of the deficit. When the number of items to be remembered during auditory presentation increased from one to three the mean reaction time of the patients to correctly identified probes increased four-fold compared with normal subjects (332 vs 76 ms). The latter value from our normal subjects compares well with previously published normative data showing an increment of reaction time of 25 to 50 ms per item in a probe identification task of short-term memory (Sternberg, 1969). In our patients there is also a sizeable increase in the SD of reaction time between the one and three-item sets when compared with normals (274 vs 6 ms). Thus even when the patients are performing correctly in identifying the matching probes, they become inordinately slowed and more variable with only a two item increase in the number of items to be remembered. These effects were seen in Case 1 with a lengthening of the string by only a single item, from just one to two. The data cannot distinguish where along the memory process the impairment occurs. It obviously is at a critical point because slowing of reaction time occurs after so few items have been presented. There is a suggestion from the SD measures in the one-item probe identification and rare target identification tasks that perhaps even the processing of single items employing auditory short-term memory may also be impaired. The deficits of memory are evident whenever the auditory system is used. For instance, in the visually presented one-item digit probe task, the reaction time for Case 1 slowed and became more variable when the probe was presented acoustically rather than visually even though the performance scores on the two tests were almost identical (Table 4). However, it may be that the deficits of short-term memory also involve visual processes as with visual presentation alone reaction times and their accompanying SD were also greater than normal (Table 3).

The reliability of reaction time measures in the digit probe identification tasks is evidenced in Case 1 who had a stationary clinical deficit of short-term memory. His reaction times were consistent on three separate assessments over a month. In contrast, Case 3 showed a normalization of the reaction time measures as the clinical manifestations of the short-term memory deficits improved. These results are certainly congruent with previously published studies of the performance of patients with conduction aphasia and deficits in auditory digit span (Shallice and Warrington, 1977). Moreover, the reaction time data from the present study complement our understanding of the behavioural consequences of impaired auditory short-term memory through the demonstration of an increase in both the absolute reaction times and their variability with increases in the number of items to be remembered.

*Event-related Potentials*

The event-related potentials accompanying correct identification of matching probes consisted of a high amplitude sustained positivity commencing at about 350 ms, reaching a plateau at 450 ms and, following auditory presentation, persisting with little decrement for more than 500 ms and for a slightly shorter duration following visual presentation. This component is comparable to the 'P300' of Ford *et al.* (1979) evoked in a similar digit probe identification task employing the visual modality. It is to be distinguished from the P300 component evoked by targets in the infrequent signal identification tasks by the shorter latency and brief duration of the latter. There is also a major difference in amplitude between the potentials evoked by stimuli not requiring an overt response by the subject; the P300 to the frequent signals in the 'oddball' task is of very small amplitude, whereas the P450 component associated with correct rejections in the digit probe identification tasks occurs with a similar high amplitude to that for hits and slightly longer latency. This difference in amplitude may be due, in part, to the different probabilities employed in the two tests. In the rare signal task the frequent stimulus occurred with a probability of 0.85, whereas in the probe identification tasks the out-of-set probes occurred with a probability of 0.5. Further differences between the potentials evoked by the two tasks occur in the early components preceding the major positivities. Event-related potentials to in-set probes consist of an initial negativity (auditory) or positivity (visual) at 150 ms followed by a negativity at about 250 ms. For auditory probes this second negativity cannot be easily distinguished from the N150 in contrast to the potentials evoked in the 'oddball' task in which a P200 component clearly demarcates the N100 from the N200.

In the probe identification tasks there are several differences between the patients' and normal controls' P450 components evoked by the matching probes. First, the mean amplitude of the patients' P450 to the probes following the presentation of the one-item string in the auditory modality is less than half of that of the control group but of equal value in the visual modality. Secondly, there is a greater mean increase in latency of the P450 component when the string length increased from one to three items in the auditory modality for the patients (201 ms) compared with the controls (64 ms). Previously published values of latency increment as a function of string length in normals using the visual modality are comparable to our normative data (Ford *et al.*, 1979).

In the patients, the latency, amplitude and even occurrence of the P450 component evoked by each presentation of the probe was quite variable. We therefore reanalysed the single trials to correctly identified in-set probes (hits) according to reaction times (fastest, middle and slowest thirds) and, where appropriate, by the position of the matching item in the preceding sequence (first, second or third) to determine the influence of these variables. For the one-item string presented in the auditory modality the patients' P450 was of larger amplitude and shorter latency in those trials associated with the fastest reaction times compared to the grand

average. These measures were substantial compared with the modest changes accompanying selective averaging by reaction times for the normal group (see figs 4, 5). Thus the patients can generate a normal amplitude P450 component to correctly identified auditory probes in the one-item task when the average is based on those trials having the fastest reaction time. However, the amplitude of this component was not comparably enhanced in the auditory three-item task, either by averaging according to reaction time or position of the matching item in the set preceding the probe.

The change in amplitude of the patients' P450 component with reaveraging according to the fastest reaction times particularly affected the earliest portion of this component, whereas the sustained portion of the positive shift was only slightly modified. This finding raises the possibility that P450 may consist of two subcomponents, similar to the segregation of the P300 component evoked in the rare signal detection task into an early P3a and late P3b component. The former has been associated with orienting (Näätänen *et al.*, 1980) and arousal, independent of an overt response to the rare signal (Squires *et al.*, 1975), whereas the latter P3b component is more intimately associated with the classification of the stimulus (Pritchard, 1981). The definition of an increase in amplitude of the early portion of P450 in the patients may reflect activity of normal arousal processes, whereas the absence of substantial growth of the sustained portion of this component may indicate a defect in the patients' ability to classify stimuli.

Averaging of individual event-related potential trials is most suitable when there is little temporal jitter of the components from trial to trial. The sensory evoked potentials of short latency, such as the auditory brainstem potentials, are an example of a sensory event-related potential having relatively constant latency for each component in each trial (Galbraith, 1984). In contrast, the late components evoked in the probe identification tasks are extremely variable in latency and this affects their amplitude in the conventional average. The use of latency-adjusted averages has been employed to compensate for the smudging effect of latency jitter in these circumstances. In the present study, some of the variability of latency of the P450 component in the patients was closely allied to reaction times. The finding in the patients of an increase in the variability of certain of the components of the event-related potentials may be an important indicator of their disorder. A similar observation of increased P300 variability has also been defined in some patients with Alzheimer's disease in the 'oddball' task (Patterson *et al.*, 1985).

The P300 component of event-related potentials has been well studied and classified as endogenous, reflecting cognitive processes and, more particularly, aspects of memory function involved in 'memory updating' (Donchin, 1981). This is based on the increment in amplitude accompanying the presentation of novel stimuli, either with regard to their global probability or to the pattern of stimuli in the immediately preceding sequence (Squires *et al.*, 1976). The finding of alteration in amplitude of a P300-like component, designated as P450 in this study, in patients with a disorder of auditory short-term memory provides support for the



concept that the component bears some relationship to the memory process. The amplitude decrement of P450 is particular to auditory rather than to visual probes and correlates well with the accompanying behavioural deficits in the auditory modality. These findings can be considered as additional evidence linking the P450 component to activity of neural circuits subserving memory. However, the present results cannot be taken as evidence of a causal link between P450 and short-term memory processes. Instead, the alteration of P450 found in these patients indicates that the disturbance in tests of short-term memory represents a disorder of memory rather than a disorder of response selection as has been suggested by Kinsbourne (1972) in this syndrome. A disorder of response selection could have been proposed to account for the poor performance had these patients demonstrated a normal P450 amplitude and latency.

It is clear that the adaptation of behavioural tasks that reflect particular cognitive functions, such as the probe identification task of short-term memory in this study, provides a more powerful analytic method than the standard infrequent target detection or 'oddball' tasks. Measures of P300 in the 'oddball' tasks were normal in our patient group (with the exception of Case 4 who could not perform the task and who did not have a P300 component) suggesting that this latter task probably puts little demand on short-term memory functions. Thus the observation of normal P300 in some patients with dementing illness using the 'oddball' paradigm should not be too surprising (Goodin *et al.*, 1978). It is not clear what cognitive function the oddball task measures, but the detection of novelty (i.e., stimulus change) would be a reasonable candidate. Such cognitive processes have not been clearly identified as being abnormal in demented patients. Certainly it would seem more appropriate to examine patients with electrophysiological measures that are relevant for their behavioural deficits. The benefits of such analyses may provide evidence for mechanisms of their cognitive disorders as well as providing objective parameters of the neural structures subserving cognition.

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## CORRELATIONS OF SUBCORTICAL CT LESION SITES AND APHASIA PROFILES

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### SUMMARY

We have analysed the aphasia profiles of 19 cases with subcortical infarction or haemorrhage. Several components of the aphasic syndromes, especially sentence length and grammatical form (together compromising fluency), ease of speech initiation, articulation, voice volume, and auditory comprehension, were individually isolated for correlation with CT lesion site. Each component had a specific lesion site correlation, and lesions in various deep periventricular white matter regions were the critical ones for all components of aphasia. Simple tabulation of lesions as cortical or subcortical, and restricting analysis to lesions of basal ganglia would both have proved inadequate to account for clinical findings. A review of 61 subcortical cases in the neurological literature for which CT and aphasia data were available supports these conclusions.

### INTRODUCTION

In the past five years interest has been rekindled in the role of subcortical structures in aphasia. In many of the original analyses of aphasia-producing lesions, a potential role of subcortical structures was recognized (Marie, 1926–8), but the recent surge in capacity for *in vivo* high resolution imaging of brain lesions has triggered a modern re-examination of subcortical structures. To this point, the several published investigations have reached little consensus on the effects of subcortical lesions or even on which types of patients to study. Thus there are reports on intracerebral haemorrhages and on infarctions, and there is one literature on 'thalamic aphasias' and another on 'subcortical aphasias'. Many investigators, either directly from their own work or indirectly by failure to confirm the observations of others, have thus far only emphasized the variability of the syndromes.

In the present report we detail our analysis of 19 cases with entirely or predominantly subcortical lesions. We have specifically excluded cases of primary thalamic infarction or haemorrhage because the available evidence suggests that thalamic lesions produce cognitive and language deficits through different patho-

physiological mechanisms than other subcortical lesions (Graff-Radford *et al.*, 1984). Our analysis will confirm the variability in the 'subcortical syndromes' but will also suggest that there are specific anatomical bases for most of the variability. We produce evidence that insular cortical lesions are not the cause of aphasia in these patients. Finally, we construct a model of the various roles of subcortical structures in aphasia and document the general validity of that model in a review of 61 previously published cases of subcortical nonthalamic aphasia.

## PATIENTS METHODS

### *Patients*

The first 17 cases to be reviewed represent every patient known to us at the Boston VA Medical Center from 1980 to 1984 who met two criteria. (1) CT demonstrated a unilateral left hemisphere vascular lesion with minimal or no involvement of cortical structures. There is one exception to this criterion, Case 14, described below. (2) Formal aphasia evaluation was performed two or more weeks after the acute illness.

All were right handed. Five were bilingual. Education was at least to the eighth grade (typically to the age of 14 yrs); most were high school graduates. No patient had a history of previous focal neurological events, but several patients had histories of alcohol abuse. The aetiology in all cases was stroke: infarction in 12 and spontaneous intracerebral haemorrhage in 5. Case 6 was included in an earlier report (Freedman *et al.*, 1984); he has been included in the present report because the location of his infarction is critical for many of our present observations. Two additional patients were included in the study. These cases had infarctions extensively involving the insula as well as partial damage of the external capsule and lateral putamen.

### *Analysis*

*Aphasia assessment.* Aphasia was assessed with the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1972), performed two or more weeks after onset of illness. Phrase length and grammatical form were used as measures of the fluency of language production. Articulatory agility was used as a measure of dysarthria. We use dysarthria to denote speech disturbances due to motor impairment; in individual cases, disorders of rate, articulatory precision, production of complex speech sounds and sound transitions may contribute to dysarthria. Prosody and volume were assessed only by clinical judgement. Auditory comprehension was measured as the overall z-score for auditory comprehension on the BDAE. Repetition was measured as the sum of the scores for the high and low probability sentences. Reading comprehension was also assessed as an overall score by averaging z-scores of the reading subtests for word-picture matching and for sentence-paragraph material. In addition, ideomotor apraxia was tested with a commonly used clinical method (Geschwind, 1975).

*CT scan localization.* CT analysis was performed by the method of Naeser and Hayward (1978), as adapted to identify specific subcortical regions by Naeser *et al.* (1982). Slice notation (B, B/W, W, etc.) follows the system used in those two reports. Simple tabulation of lesions as nuclear or white matter (Wallesch *et al.*, 1983) and unelaborated notations about white matter extension (Cappa *et al.*, 1983) are not adequate to resolve the clinical-anatomical questions at the heart of this report. We believe that very small changes in lesion size and/or lesion site can have dramatic effects on language. We therefore specifically analyse each CT scan for evidence of damage to several discrete brain regions, both nuclear and white matter. These included the following regions (some have been given our own labels for shorthand reference).

1. Putamen: this nuclear structure is represented on slices B, B/W and W; the genu of the internal capsule was used to demarcate anterior and posterior putamen.

2. Head of caudate: this structure is seen on slices B, B/W and W.
3. External capsule: this is situated lateral to the putamen on slices B, B/W and W.
4. Insular cortex: this includes all cortex on the medial surface of the sylvian fissure on slices B, B/W and W.
5. Internal capsule: several distinct regions can be identified on slices B, B/W and W: (a) the anterolateral half of the anterior limb (ALIC) (fig. 1); (b) the posteromedial half of the anterior limb (fig. 1); (c) the genu (GIC); (d) the posterior limb (PLIC).
6. Periventricular white matter (PVWM): (a) anterior PVWM extension: on slices B and B/W, the white matter anterior to the ALIC and deep to Broca's area (fig. 2); on slice W, the white matter anterior to ALIC and deep to the lowest portion of the motor cortex; (b) extra-anterior PVWM extension: on slices B, B/W and perhaps W, this is the white matter region which extends anteriorly from deep to Broca's area across projections of the genu of the corpus callosum (fig. 2); (c) anterior superior PVWM extension: on slices SM and SM + 1, this is the white matter region anterolateral to the anterior portion of body of the lateral ventricle (fig. 3); (d) superior PVWM extension: on slices SM and SM + 1, this is the white matter adjacent to the anterior two-thirds of the body of the lateral ventricle (fig. 3); the thin body of the caudate nucleus lies between the white matter and the ventricle, but cannot always be distinguished clearly on CT; (e) posterior PVWM extension: on slices SM and SM + 1, this is the region adjacent to the posterior third of the body of the lateral ventricle and on slice W, the region adjacent to the atrium of the lateral ventricle (fig. 3).

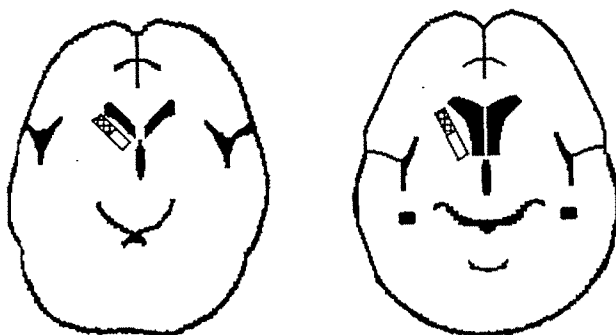


FIG. 1. Diagram of CT scan at slices B (*left*) and B/W (*right*). Cross-hatched area is the anterolateral half of the anterior limb of the internal capsule (ALIC). Open area is the posteromedial half of the ALIC.

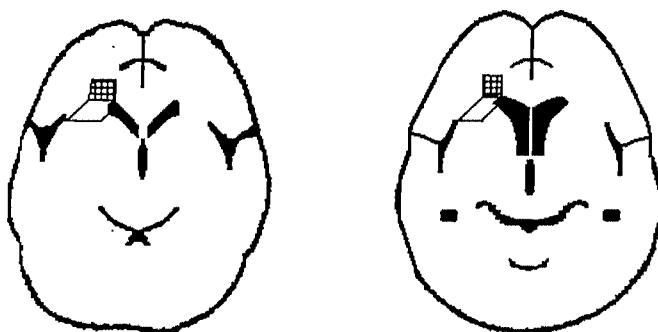


FIG. 2. Diagram of CT scan at slices B (*left*) and B/W (*right*). Cross-hatched area is extra anterior periventricular white matter (PVWM) extension. Open area is the anterior PVWM extension.

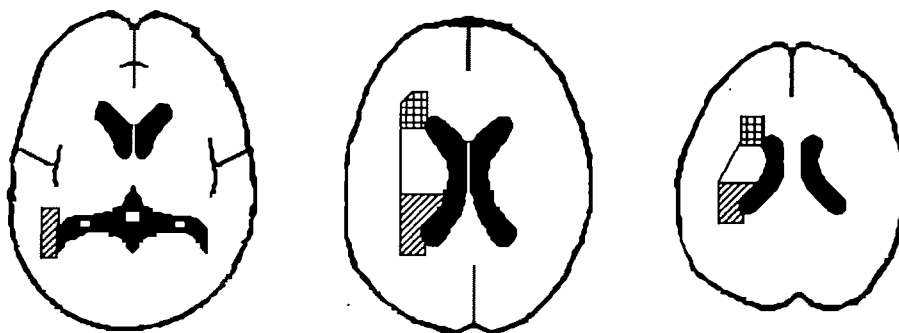


FIG. 3. Diagram of CT scan at slices W (*left*), SM (*middle*) and SM + 1 (*right*). Cross-hatched area is anterior-superior PVWM. Open area is superior PVWM. Slashed area is posterior PVWM.

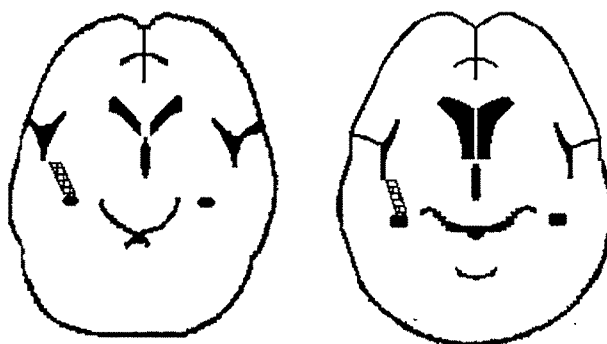


FIG. 4. Diagram of CT scan at slices B (*left*) and B/W (*right*). Cross-hatched area is the temporal isthmus.

7. Temporal isthmus (TI): on slices B and B/W, this is the small area between the posterior limit of the sylvian fissure and the temporal horn of the lateral ventricle (fig. 4).

Scans available for analysis were performed at variable times after the stroke. When possible, a scan more than four months postonset was used. In the figure legends, the time postonset is noted. Scan slices were 10 mm. The CT analysis may miss small lesions.

## RESULTS

The clinical findings and language capacities of all patients are summarized in the Appendix. A variety of language behaviours and lesion distributions were observed; there is no single all-encompassing conclusion to be reached from this study as to the relationships of subcortical lesions to aphasia. Instead, there are several independent observations to be emphasized. These results will be amplified by a review of the relevant literature in the Discussion.

### *The Role of Vascular Aetiology*

The 5 patients who had had an intracerebral haemorrhage (ICH) all had fluent aphasia. Of the 12 patients with infarction, 7 were fluent and 5 were nonfluent.

Both cases with a 'subcortical Wernicke's aphasia' had had an ICH. Careful inspection of CT lesions suggests two reasons to support a conclusion that these findings represent the effects of specific lesion sites and not aetiology. First, none of the patients with ICH had extension of the lesion into the anterior or superior PVWM. Damage to these regions has a high association with nonfluency (*see below*), and there are reported cases of ICH with anterior, extra-anterior and superior extensions with nonfluent aphasia (Hier *et al.*, 1977). Since none of our cases with ICH had that pattern of lesion extension, it is not surprising that none was nonfluent. Secondly, the topography of lesions following ICH is not restricted to discrete vascular territories, and therefore lesions following ICH may have distributions not possible or, at least, not common after infarctions. The only cases in our series in which lesion extension was *limited* to the deep inferior plane posterior to the putamen and across the PLIC and TI were 2 of the cases of posterior putaminal ICH. There were cases of infarction in which that region was damaged but always in association with larger lesions also involving anterior and superior extension.

#### *The Role of Damage to Insular Cortex*

Several of our patients with subcortical lesions had CT evidence of involvement of the cortex of the medial insula. Other investigators have suggested that this damage might be the cause of speech and language disturbances (Cappa *et al.*, 1983). We therefore analysed 2 patients (Appendix, Cases 1, 2) with lesions restricted to insular cortex and the immediately subjacent extreme/external capsule region (fig. 5). These 2 patients had normal speech. Both had mild fluent aphasia with word-finding difficulty and rare phonemic paraphasias in conversation. In 1, phonemic paraphasias increased in repetition; in the other, when reading aloud. Both were agraphic. In sum, infarction of insular cortex and subjacent white matter produces a mild fluent aphasia, most similar to, in classical terminology, a conduction aphasia (Benson *et al.*, 1973). This is not the pattern of the subcortical cases discussed below with one exception (Case 19), for which a specific anomaly of the lesion site is the basis.

#### *The Role of Small Lesions in Striatum, Anterior Limb Internal Capsule and/or PVWM*

One patient (Case 3) had a small lesion in the anterior part of superior PVWM with a small extension into ALIC and anterior putamen. He had only very mild and transient word-finding problems. Speech was marked by a mild loss of normal prosodic smoothness—hesitations and slow transitions between words and syllables, and the loss of his previously (by history) dense Bostonian accent. There was complete recovery of language in one month. Two patients had small lesions centred on the anterior putamen and/or various parts of the anterior limb internal capsule (ALIC) and the head of the caudate (Appendix, Cases 4, 5). Case 4 had a very mild disorder of word finding, as well as a reduction in spontaneous output.



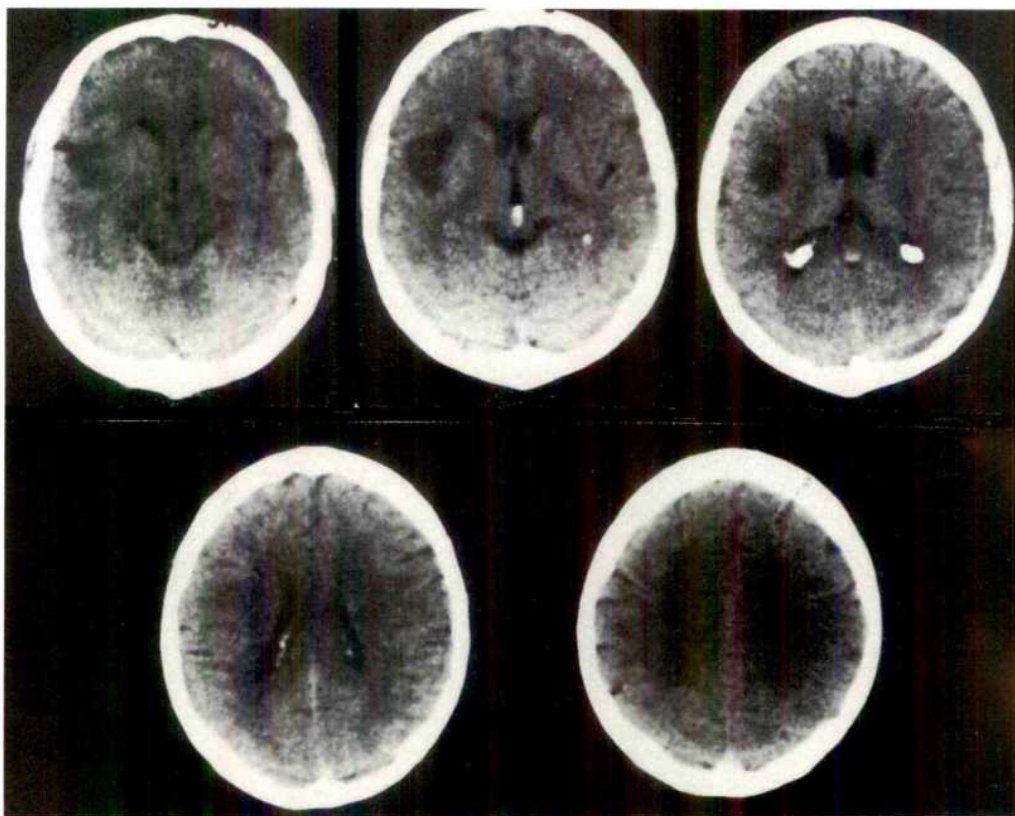


FIG. 5. CT without contrast two weeks after onset in *Case 1* showing a hypodense area (infarction) involving much of the insular cortex and the structures immediately medial to the insula, i.e., the extreme capsule, claustrum, external capsule and the most lateral putamen. There is no involvement of the caudate, internal capsule, medial putamen, or any region of PVWM. Clinical syndrome: no dysarthria and normal voice volume; conduction aphasia; no hemiparesis. *Case 2* had very similar lesion and clinical profile.

At three weeks after onset there were no abnormalities on the BDAE, but his narrative descriptions were sparse, and word list generation was reduced. The CT of this patient (fig. 6) demonstrated a small lesion in the head of the caudate, anterior putamen, ALIC and of the anterior-superior PVWM. There was no facial paresis. This implies less motor system involvement and may account for the absence of prosodic disturbance. Comparison with *Case 6* (below) will clarify the clinical-anatomical findings in this case. *Case 5* had more extensive damage to putamen and ALIC. A small lesion was also present in the superior PVWM and GIC (fig. 7). There was a dense facial paresis but no arm or leg weakness. Speech was very abnormal, with articulation, prosody and volume all impaired. Paraphasias were, however, very uncommon, even in repetition. Comprehension was impaired at the level of complex material or syntax-dependent material. This patient had the smallest lesion with persistent aphasia in our series.

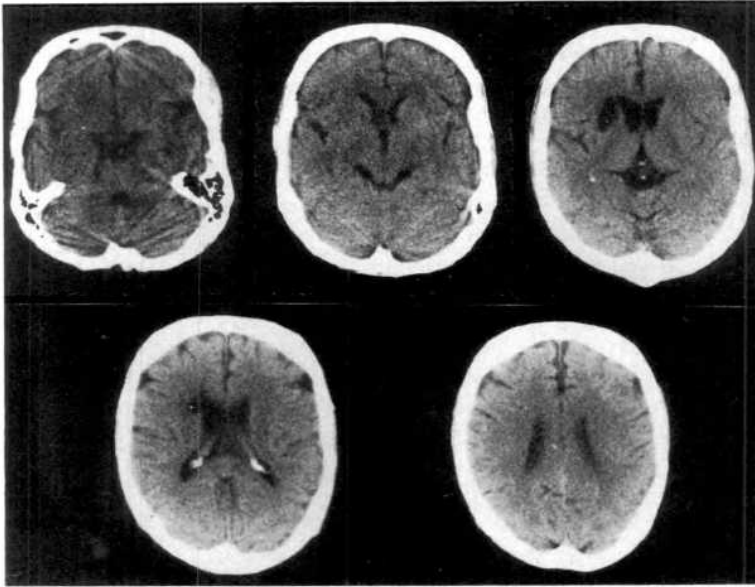


FIG. 6. CT without contrast two weeks after onset in *Case 4* showing a small hypodense area (infarction) in the head of the caudate nucleus, anterior putamen, ALIC and the anterior-superior (AS) PVWM. Clinical syndrome: no dysarthria; mild transcortical motor aphasia; no hemiparesis.

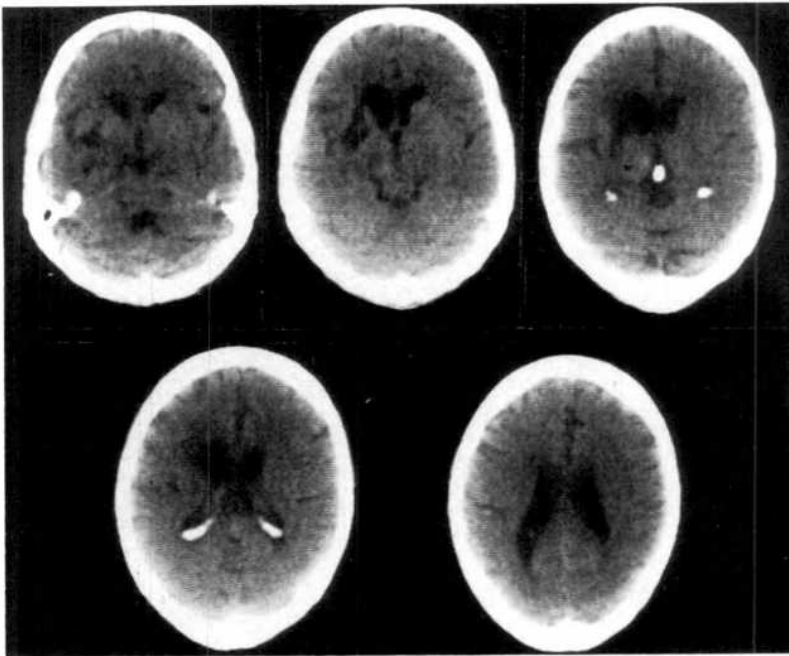


FIG. 7. CT without contrast four weeks after onset in *Case 5* showing a hypodense area (infarction) in the head of the caudate, with a large lesion in the putamen, ALIC, GIC, and a small lesion in superior PVWM. Clinical syndrome: dysarthria; hypophonia; fluent aphasia; facial paresis only. Compared with *Case 4* (fig. 6), there is a more extensive lesion in the caudate, putamen, ALIC and superior PVWM.

*Lesions of the Anterior Superior PVWM*

Case 6 was included in a previous report (Freedman *et al.*, 1984). We include him in this report because his findings exemplify the specific effect of lesion extension into the anterior-superior PVWM. He was mute for a few days and then had extremely sparse spontaneous speech, mild word-finding difficulties, markedly reduced word-list generation and reduced narrative capacity. Articulation and prosody were normal. He recovered rapidly, although spontaneous speech remained sparse. In traditional terminology, his disturbance was a mild transcortical motor aphasia (Freedman *et al.*, 1984). On CT, he had a small lesion in the anterior-superior PVWM and the white matter deep to the middle frontal gyrus (fig. 8). Case 4 (fig. 6), as discussed above, had a very similar language profile. In that case, there was a similar, although smaller lesion extension into the anterior-superior PVWM plus a small lesion in the head of the caudate. We believe that the lesion extension into anterior-superior PVWM was the primary lesion responsible for the clinical profile seen in both Cases 4 and 6.

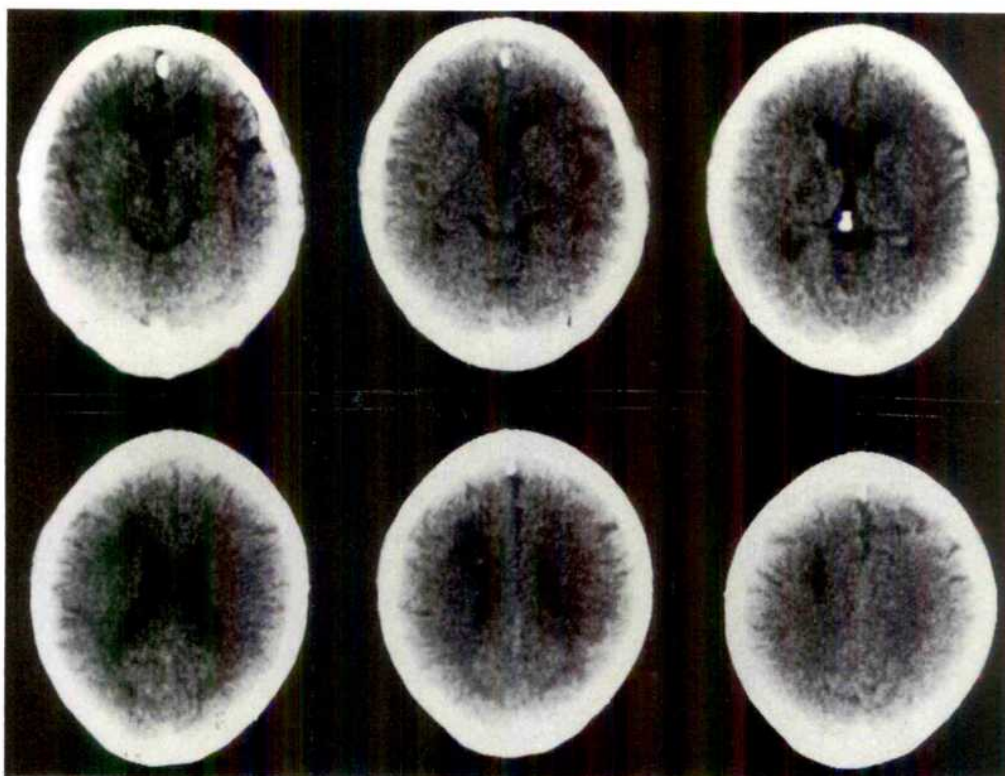


FIG. 8. CT without contrast performed one week after onset in Case 6 showing a hypodense lesion (infarction) in the anterior-superior (AS) PVWM (slices SM, SM+1). Clinical syndrome: no dysarthria; mild transcortical motor aphasia; no hemiparesis. Note that the AS PVWM lesion in Case 4 (fig. 6) has a similar, although less extensive, distribution.



*Capsular-putaminal Lesions with Various Anterior and Superior Extensions*

Two patients (Cases 7, 8) had larger lesions with extensive destruction of the putamen, ALIC, GIC and head of caudate, with extension of the lesion into the anterior, superior and anterior-superior PVWM areas (fig. 9). In both cases, there was severe dysarthria. Language was relatively fluent in structure, but spontaneous language was often sparse and restricted to short phrases. Language was always grammatically correct. Although usually simple, some complex grammar was detected. Repetition defects were usually omissions from longer targets. Comprehension was impaired only at the level of complex material or of syntax. These deficits were stable over years.

One patient (Case 9) had a similar lesion except that the anterior and inferior elements were not present: there was no lesion of the ALIC on the lower CT slices (slices B and B/W), or of most of the head of the caudate nucleus (fig. 10). Case 9 differed clinically from Cases 7 and 8 by having normal articulation.

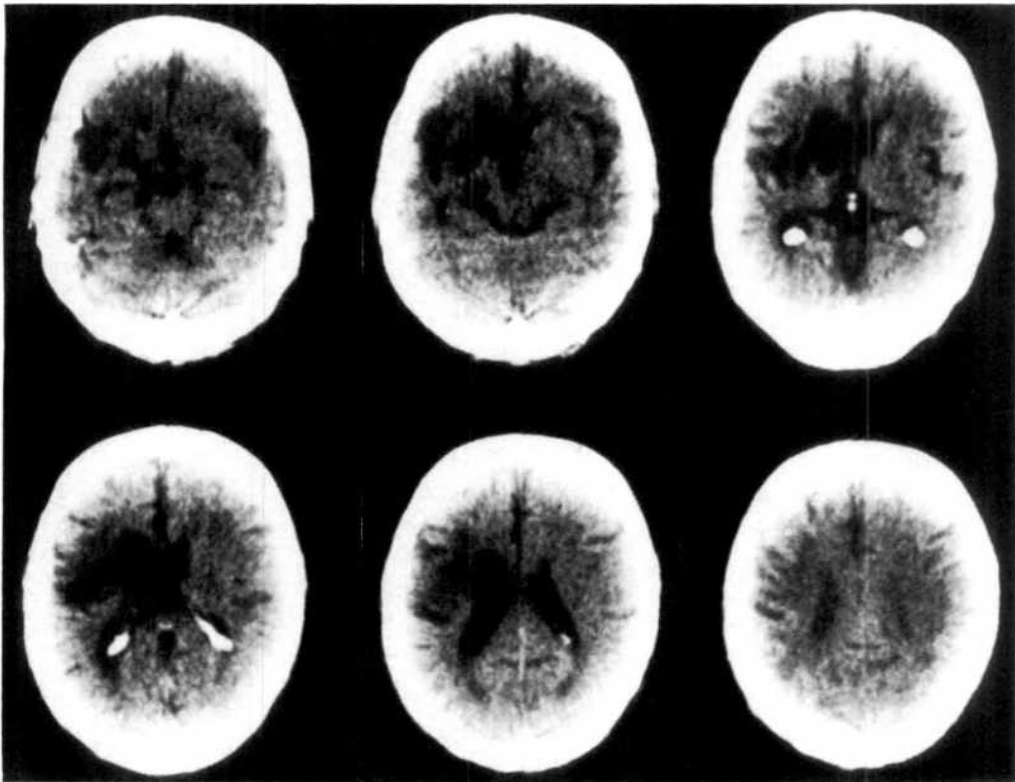


FIG. 9. CT without contrast performed nine months after onset in Case 7 showing a large hypodense lesion (infarction) in the head of the caudate, putamen, ALIC, anterior PVWM, superior PVWM and anterior-superior PVWM. There is some abnormality in insular cortex. There is considerable secondary atrophy reflected in expansion of the left frontal horn and sylvian fissure. Clinical syndrome: dysarthria; grammatical speech; hemiplegia. Case 8 had very similar clinical and lesion profiles.

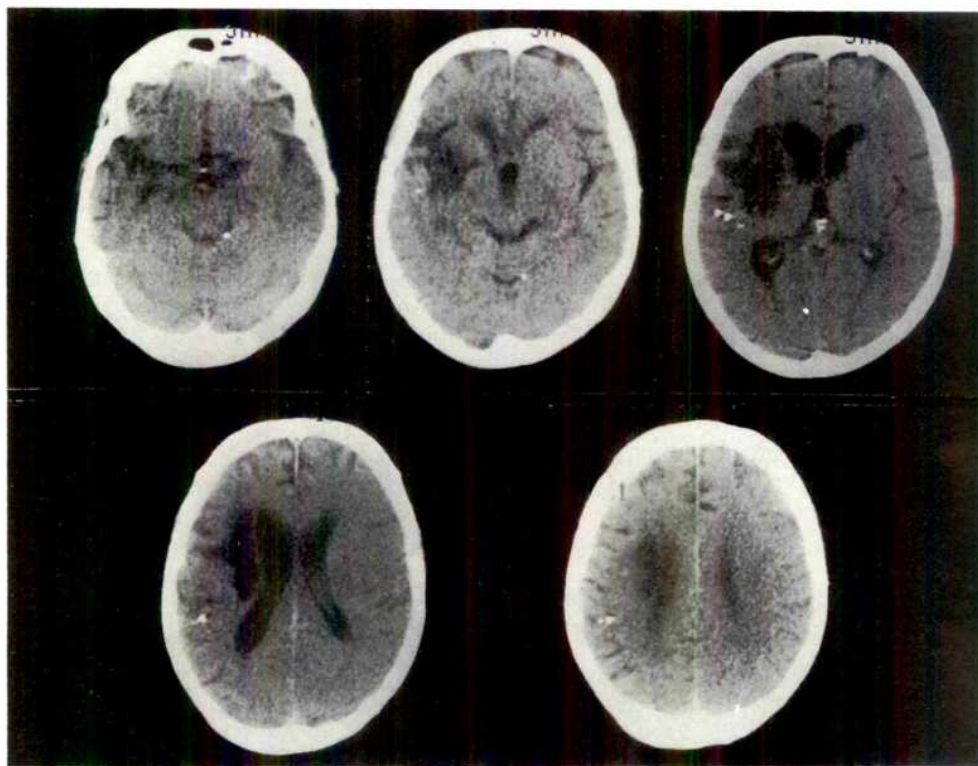


FIG. 10. CT without contrast performed four months after onset in *Case 9*, showing a hypodense lesion (infarction) in part of the head of the caudate with an extensive lesion in the left putamen, parts of the ALIC, anterior PVWM (slice W only), and superior PVWM. Clinical syndrome: no dysarthria; hypophonia; transcortical motor aphasia; hemiplegia. Note that compared with *Case 7* (fig. 9), the inferior and anterior structures of the head of the caudate, ALIC and white matter deep to Broca's area (anterior PVWM at slices B and B/W) are not involved.

*Case 10* had a lesion similar to *Cases 7* and *8* but with extra-anterior PVWM. His initial presentation was as a global aphasic. Within months, auditory comprehension improved to a level of zero on the BDAE z-score, and deficits were only noted on complex material or with syntax. *Case 10* did, however, remain very nonfluent.

#### *Capsular-putaminal Lesions with Anterior, Superior and Posterior Extension*

Three patients (*Cases 11–13*) had lesions involving the putamen, ALIC, GIC, head and body of caudate with extension of the lesion into anterior, superior and anterior-superior PVWM. The lesions in these cases differed from that of *Case 10* because they also extended posteriorly, behind the putamen and across the TI (fig. 4). In 2 cases, the lesions spread from the TI to involve deep lobar white matter (*Cases 12, 13*) and or even scattered areas of inferior temporal cortex (*Case 13*, fig. 11). In 1 patient there was variable but definite involvement of some posterior

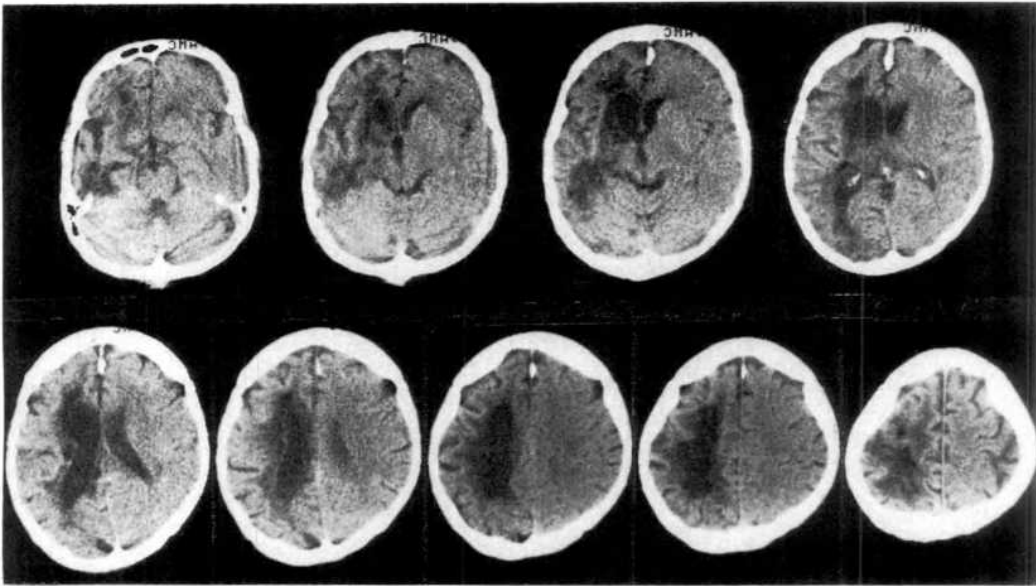


FIG. 11. CT without contrast four months after onset in *Case 13* showing a hypodense area (infarction) involving the entire left putamen, the ALIC, the PLIC, head of caudate, anterior and extra-anterior PVWM, anterior-superior and superior PVWM, posterior PVWM and temporal isthmus. There is also involvement of deep parietal white matter and inferior temporal and temporo-occipital cortex. Clinical syndrome: global aphasia; hemiplegia.

insular cortex and patchy involvement of cortex in more superior parts of the parietal lobe (*Case 12*). One patient (*Case 14*) had a cortical lesion in Wernicke's area, but in association with a large subcortical lesion in the same extensive distributions as *Case 11*. All patients were hemiplegic. Their very limited and totally nonpropositional speech output (minimal counting and yes/no) was dysarthric and hypophonic. It is probable that some part of the clinical findings in each of these patients might have been due to the patchy cortical lesions in the temporal lobe or superior parietal lobe, but in traditional terminology, all 4 patients had severe global aphasia (Goodglass and Kaplan, 1972) and only the subcortical lesions can account for the severe language deficits.

#### *The Role of Predominantly Posterior Lesion Extension*

Two patients (*Cases 15, 16*) had lesions involving the posterior putamen with extension back into the temporal isthmus. Both patients had had ICH; the reasons that a lesion in this distribution will usually be due to ICH were reviewed above. Both patients had impaired alertness for several weeks but were then fully testable. Articulation was near normal, but both were extremely hypophonic. Both had fluent logorrhoeic neologistic language. Even when apparently alert and attentive, both showed marked short-interval fluctuations in auditory comprehension, although *Case 16*, even at his best, was always very impaired. Repetition and reading comprehension were very impaired in both. Acute CT scans showed large



haemorrhages centred in the lateral putamen with mass effect but no extension to the caudate, ALIC, or to any anterior or superior PVWM regions. There was, however, a dramatic posterior extension across the PLIC and temporal isthmus and up into the posterior PVWM (fig. 12). Late scans demonstrated primarily ventricular enlargement but in an asymmetric pattern suggesting persistent injury to TI and adjacent posterior PVWM (fig. 13). Both patients had permanent dense hemiplegias and hemianopias, further supporting damage to posterior PVWM and/or posterior limb of the internal capsule and TI.

*The Role of Lesions in Putamen without Posterior Extension*

Two patients (Cases 17, 18) had lesions in the putamen but without posterior extension. In both patients the only language deficit was mild word-finding difficulty, and by two months after onset, neither patient had any language abnormality. In both cases, acute CT scans showed large haemorrhages centred in the lateral

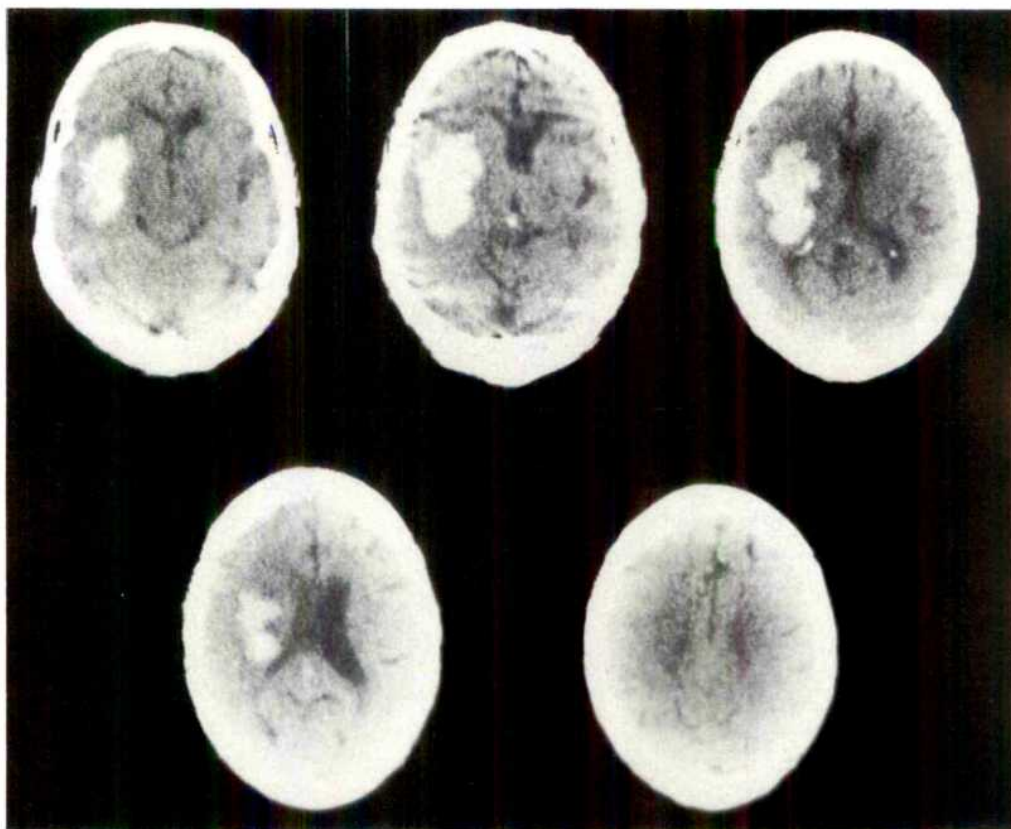


FIG. 12. Acute CT without contrast in Case 15 showing a large high density lesion (haemorrhage) in the putamen, posterior external capsule area, PLIC, TI and posterior PVWM. Note that, despite the size of the haemorrhage, the ALIC, caudate, anterior PVWM and superior PVWM are not involved. Clinical syndrome: no dysarthria; hypophonia; Wernicke's aphasia; hemiplegia.

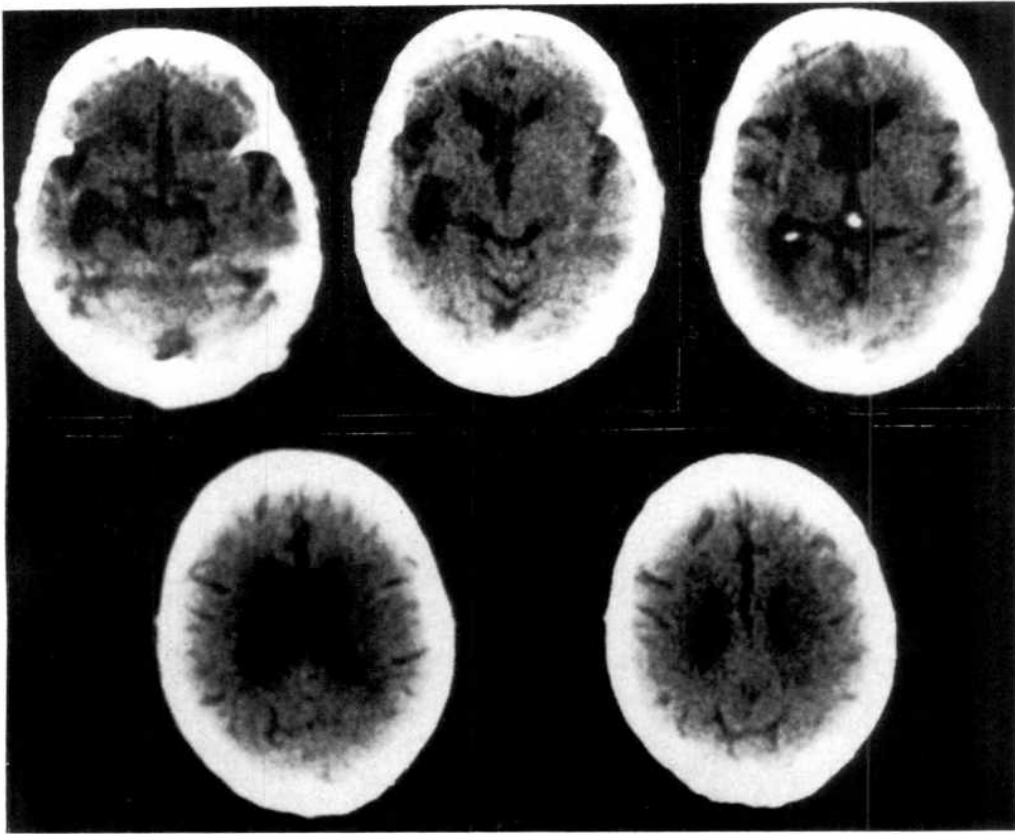


FIG. 13. Repeat CT without contrast performed eight weeks after onset in *Case 15* showing no definite lesion. The lateral ventricles are enlarged, left greater than right, with marked ballooning of the left temporal horn and atrium. The enlarged ventricle and/or hypodense lesion (resolved haematoma) extend towards the posterior putamen across the area where the TI is located.

putamen with mass effect but no direct extension into ALIC, anterior PVWM, anterior-superior PVWM or TI (fig. 14). Case 17 had persistent hypophonia without dysarthria but no other neurological deficits. A late CT demonstrated no definite lesion, but slight enlargement of the left frontal horn. Case 18 had persistent dense hemiparesis but no speech disturbance; a late CT demonstrated a small lesion in the posterior portion of superior PVWM. The small residual lesions on CT are compatible with the normal language examination at two months after onset, but we wish to emphasize the absence of any significant aphasia at a time when there was almost complete involvement of the left putamen by an acute haemorrhage. This is not simply an artefact of aetiology because similar haemorrhages involving less of the putamen, but extending posteriorly, produced profound aphasia, as described above for Cases 15 and 16.

Case 19 also had an ICH in the region of the lateral putamen with mass effect but no direct extension into ALIC, anterior PVWM, superior PVWM, anterior-



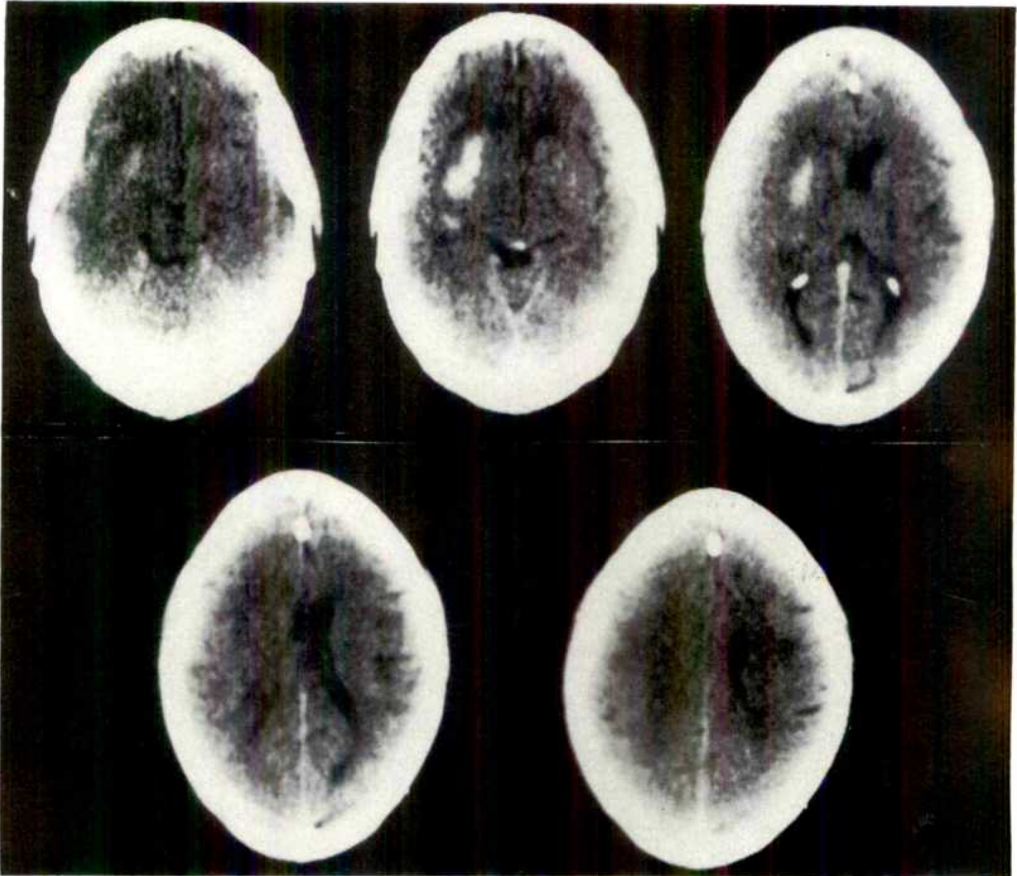


FIG. 14. Acute CT performed without contrast in *Case 17* showing a high density lesion (haemorrhage) in the putamen with slight extension laterally. There is no lesion in the caudate, ALIC or any PVWM region. Clinical syndrome: no dysarthria; mild hypophonia; minimal aphasia (anomia); no hemiparesis. Acute CT in *Case 18* revealed a very similar lesion, except for some involvement of the superior PVWM which probably accounted for his residual hemiplegia.

superior PVWM or TI (fig. 15); there was some extension into posterior PVWM. This ICH was centred in the lateral putamen and, unlike Cases 17 and 18, in Case 19 the ICH had a marked extension into the external capsule with undercutting of the insular cortex. Coming full circle to Case 1, this patient had a well-articulated fluent paraphasic output with very paraphasic repetition-conduction aphasia in traditional terms (Benson *et al.*, 1973). Unlike most patients with traditional conduction aphasia, this patient had persistent hypophonia and right hemiparesis.

#### *Synthesis of the Results*

The results of this study lead directly to a model of brain-behaviour relationships for subcortical structures and speech and language. This model of brain-behaviour

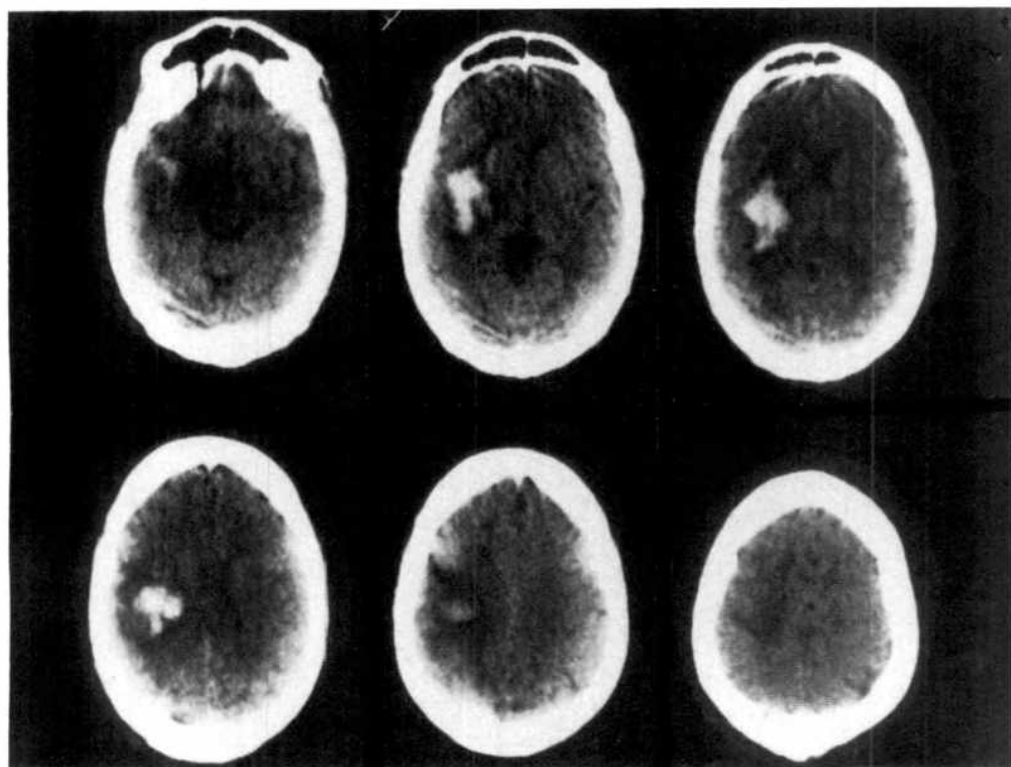


FIG. 15. Acute CT in *Case 19* showing a high-density lesion (haemorrhage) in the left putamen. Note that the CT scan is at a near-horizontal angle and that there is no involvement of the TI on the lowest cut, and that the only PVWM involved is posterior. The lesion extends lateral to the putamen, involving the external/extreme capsule and insular cortex as well as posterosuperiorly, to include posterior PVWM. Clinical syndrome: no dysarthria; hypophonia; conductor aphasia; hemiparesis.

relationships should, however, be consistent with the reports of other investigators. In the Discussion, we review its compatibility with previously reported cases.

*A model of the brain-behaviour relationships of subcortical structures.* Fig. 16 summarizes our analysis; we shall build the model one structure at a time.

Lesions limited primarily to the putamen (Cases 17 and 18 in the acute phase) or to the head of the caudate nucleus (Case 4) resulted in no language disturbance or in only mild word-finding difficulties. Striatal lesions which were small or involved the more anterior elements (head of caudate and anterior putamen) did not produce speech disturbance, but lesions which involved posterior putamen (Cases 15, 16, 17, 19) or the putamen extensively (Cases 5, 9) were associated with hypophonia.

Additional small involvement of the ALIC still produced no speech or language disturbance (Case 4). Limited involvement of the superior PVWM also did not result in language disturbance or significant speech disturbance except perhaps

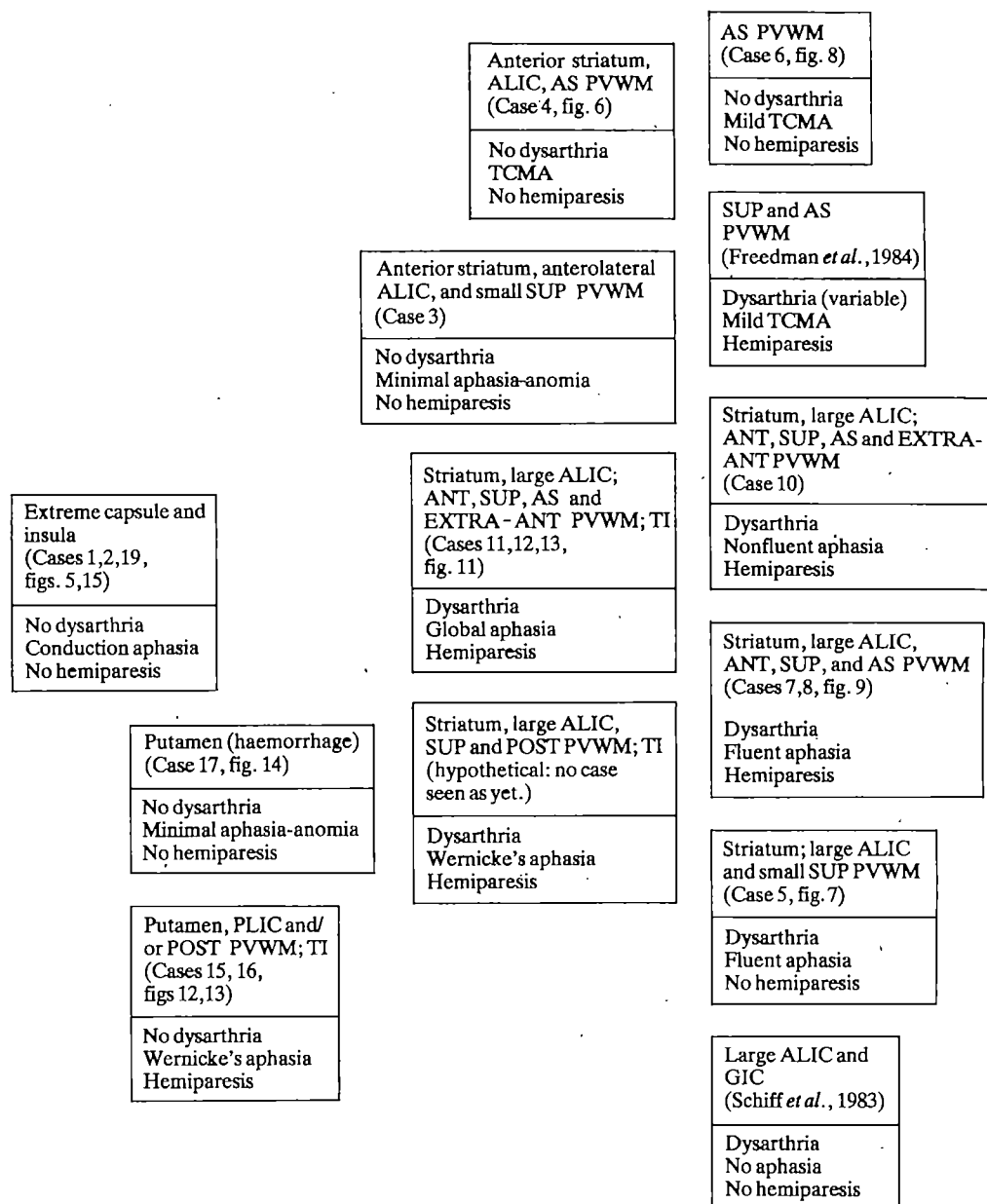


FIG. 16. Schematic outline of the clinicoanatomical relationships of subcortical lesions and aphasic disorders. With deference to the 'diagram-makers' of history, this scheme is meant only to guide the reader's mental reconstruction of the anatomical interrelationships. Abbreviations are discussed in the Methods section.

mild dysprosody (Cases 3, 18). Any further lesion extension beyond these limited structures resulted in speech/language impairments, although some were quite subtle.

Involvement of anterior-superior PVWM produced reduction in language production—sparse, limited output with hesitation and slow initiation—but no overt abnormalities in language (Case 6), even if associated with some striatal/lateral ALIC damage (Case 4). We have previously suggested (Freedman *et al.*, 1984) that the damage to the anterior-superior PVWM and perhaps the anterior portions of the superior PVWM may reduce language output by destruction of connections from the supplementary motor area to Broca's area; injury to these connections reduces the limbic input to language areas and thus the drive to speak, while leaving the cerebral mechanisms of speech and language undisturbed. More extensive lesions in the deep frontal white matter result in classical transcortical motor aphasia (TCMA). The profile of classical TCMA was not altered either by anterior striatal (Case 4) or small superior PVWM lesion extension (Case 9).

Extensive injury to the striatum, posterior-medial portion of ALIC and anterior-superior PVWM with slight injury to the superior PVWM was the smallest subcortical lesion associated with persistent major language abnormalities (Case 5; fig. 7). Word-finding deficits, occasional phonemic paraphasias and mild disturbance of comprehension (of complex material or syntax) define the aphasia. Pathophysiological mechanisms have been suggested (Damasio *et al.*, 1982; Naeser *et al.*, 1982), but are not known for certain. Marked dysarthria in Case 5 and in all other subcortical cases where dysarthria was observed was secondary to a large lesion in the posteromedial ALIC and GIC and/or in the superior PVWM. These lesions probably disrupted all descending outputs from Broca's area and inferior motor cortex (Schiff *et al.*, 1983). The region at the junction of the posteromedial ALIC and GIC seems particularly important for articulation (Fisher, 1979; Schiff *et al.*, 1983). If either the ALIC or the superior PVWM is spared in these cases, articulation may be preserved.

If damage to the anterior PVWM and more extensive damage to the superior PVWM was added to the smallest persistent lesion with aphasia described above (Case 5) aphasia was much more severe (Cases 7, 8). Language was basically fluent in structure with no overt agrammatism and with clear capacity for lengthy phrases, yet the patients had a tendency to use only short phrases and a restricted range of grammatical construction. There was marked hesitancy and slowness. Paraphasias were rare. When combined with marked dysarthria, these qualities may well satisfy some investigators' criteria for nonfluency (Damasio *et al.*, 1982). We used two other criteria for nonfluency: a constant restriction in phrase length and the use of agrammatical structures (Goodglass and Kaplan, 1972). That level of nonfluency may require extra anterior PVWM extension past the frontal horn, including portions of the genu of the corpus callosum (Case 10). We have not examined enough cases with small differences in anterior and extra-anterior PVWM extension. The exact anatomical foundations of full nonfluency (as defined above) after

anterior subcortical lesions must remain uncertain at present (*see also* Knopman *et al.*, 1983).

If a lesion of the putamen was complicated only by posterior extension across the TI, there was fluent aphasia with neologistic output and impaired comprehension (Cases 15, 16). The pathophysiology of this syndrome is unknown. We have previously suggested (Naeser *et al.*, 1982) that the lesion of TI disrupts the thalamic-temporal pathways and that this disruption results in neologistic paraphasia and impaired auditory comprehension. If the lesion of TI is combined with the lesion of the posterior PVWM which damages auditory association callosal pathways from the right hemisphere to Wernicke's area (Damasio and Damasio, 1979), auditory comprehension defects may be more persistent. We have analysed our cases to try to confirm this relationship, but too few cases with adequate CT resolution have left this unresolved. With either lesion extension profile (TI alone or TI and posterior PVWM), the accompanying neurological signs may include hypophonia—perhaps due to injury to the posterior putamen—and hemiplegia (probably due to a lesion in PLIC). These signs distinguish the subcortical from the cortical Wernicke's aphasia.

In our series, if one lesion or a series of primarily subcortical lesions damaged the striatal-ALIC area plus the extra-anterior PVWM, anterior PVWM, anterior-superior PVWM, superior PVWM and TI, there was a severe global aphasia (Cases 11–13). Subcortical extension of lesions may explain some other cases in which reference to the cortical injury alone cannot account for the aphasia profile (e.g., Case 14).

Finally, if the subcortical damage was primarily lateral to the putamen, another entire system of structures was involved: insular cortex, extreme capsule, claustrum and external capsule. Damage in this area resulted in typical conduction aphasia: word finding impairments with phonemic paraphasias, increased by repetition and/or reading aloud (Cases 1, 2, 19).

## DISCUSSION

### *Is Our Model Compatible with Previously Reported Cases?*

There have been numerous reports in recent years of subcortical lesions causing aphasia. If the model that we have suggested is valid, it should account for previously reported cases. In our earlier report (Naeser *et al.*, 1982) we tentatively identified three syndromes, labelled capsular-putaminal (CP) with anterior-superior extension, CP with posterior extension, and CP with both extensions. The model we suggest now is certainly compatible with these syndromes. CP with both extensions is the same lesion as in our current Cases 11–13: these cases have global aphasia due to simultaneous damage to frontal efferent, callosal and afferent auditory pathways. CP with posterior extension alone is the same lesion as in our current Cases 15 and 16. We discussed above the probable pathophysiological

mechanisms of this syndrome. CP with anterior-superior extension is the same lesion as in our Cases 5, 7 and 8. In the current report we have analysed more closely the various factors contributing to dysarthria, speech initiation block and hesitancy, and frank nonfluency. These are all features of various specific lesion profiles of anterior, extra-anterior, anterior-superior and/or superior PVWM extension.

In another earlier report (Alexander and LoVerme, 1980), we described the language deficits seen in cases of deep intracerebral haemorrhage. In that report we focused on the location of the nuclear damage (putamen or thalamus), and we were unable to differentiate decisively between 'putaminal aphasia' and 'thalamic aphasia'. We confirmed earlier reports (Mohr *et al.*, 1975) of the remarkable nonaphasic elements of behaviour in the patients with thalamic haemorrhages—dramatic fluctuations in the findings on language examination, attentional disturbances, abnormal affect and memory impairment. Similar changes were also described in the putaminal aphasias (Hier *et al.*, 1977), and most studies of deep intracerebral haemorrhage report those findings, even in primary haemorrhage in the head of the caudate (Stein *et al.*, 1984). In retrospect, many findings, which seemed unaccountable in the earlier report, can now be resolved with the present model. First, there was a rough relationship between the size of putaminal haemorrhage with aphasia; we did not have a clear explanation for which structures were damaged by the larger haemorrhages. We now suggest that as these haemorrhages enlarge in the anteroposterior (parasagittal) and dorsoventral (vertical) planes, there is increasing likelihood of disruption of key white matter pathways. Secondly, in the earlier report (Alexander and LoVerme, 1980), it was an unexpected observation that 2 of the 3 cases of persistent Wernicke's aphasia followed putaminal haemorrhage. Our present findings suggest that this is caused by lateral putaminal haemorrhage when there is posterior extension in the parasagittal plane (as our Cases 15 and 16). Thus although attention had been drawn to these cases by the earlier reports of 'thalamic aphasia', our cases of thalamic haemorrhage overall showed better recovery than the putaminal haemorrhages. Thalamic haemorrhages do not usually have the lateral extension necessary to damage the structures reviewed in this report (Walshe *et al.*, 1977), but some large lateral thalamic haemorrhages may be able to reach at least the temporal isthmus—thus the occasional persistent Wernicke's aphasia after thalamic haemorrhage (Alexander and LoVerme, 1980). Speech disturbances (dysarthria and hypophonia, together giving speech a mumbling quality) were equally prominent after thalamic and putaminal cases. Most investigators have pointed out the motor relationships of the cortical-striatal-pallidal-lateral thalamic-ALIC-cortical loop (Alexander and LoVerme, 1980; Damasio *et al.*, 1982; Gorelick *et al.*, 1984), and have suspected that the similarity in the speech disturbance could come from injury within various parts of this loop.

We believe that the pathophysiological mechanisms of aphasia after thalamic lesions differ from the putaminal cases. Subsequent reports have suggested two constellations of thalamic infarcts that produce language disturbances. One lesion

involved anterior thalamic nuclei (Graff-Radford *et al.*, 1984), and one involved lateral thalamic nuclei (Gorelick *et al.*, 1984). Thalamic infarctions are due to disease of the posterior circulation, and consequently cannot involve the nuclear or white matter structures which we suggest are critical for our model. We have excluded thalamic lesions from this report and have considered them elsewhere in a different context (Mandell *et al.*, 1985).

Cappa *et al.* (1983) reviewed 12 patients with subcortical infarctions. It is difficult to assess precisely the lesion distributions as only 1 or 2 CT sections are published for each case. Nevertheless, most of their cases fit our model. Cases 1-1 and 2-2 had fluent paraphasic aphasia with impaired repetition; both probably had mild conduction aphasias. Both had had lateral putaminal haemorrhages involving subinsular white matter; neither had anterior or posterior extensions, but superior extension could not be assessed from the published CT scans. These patients clinically resemble our Case 19; the lesion localization is precisely that suggested by others (Damasio and Damasio, 1980) for one subtype of conduction aphasia. Case 2-3 of Cappa *et al.* had a language profile suggesting TCMA. The lesion was an ICH, described as head of the caudate and ALIC, but the only published CT is a section above those structures with a lesion in the anterior-superior PVWM. This is, of course, precisely the profile of our Case 6 and compatible with our earlier reports on TCMA (Freedman *et al.*, 1984). Cases 1-2 and 2-4 apparently had only mild anomic aphasias; both had small infarctions of the posterior putamen (and in 1 case, PLIC). These cases are similar to our Case 17. Case 2-1 had a nonfluent aphasia with impaired repetition and mild comprehension impairment; CT demonstrated an infarct of the putamen, ALIC, head of caudate and anterior and superior PVWM. This case is similar to our Cases 5, 7 and 8 and is one of the profiles of CP infarction with anterior and superior extension. The patient of Cappa *et al.* had normal articulation for which we cannot account; publication of lower CT sections of ALIC might have clarified that exception from our model. Cases 1-3 to 1-6 were not aphasic, but they had small lacunar lesions of putamen or internal capsule; in the single CT section published for each case, there was no lesion extension. Case 2-6 in this study was also not aphasic. He had been referred because another physician had 'suspected' aphasia. When examined 57 days after onset, there was no aphasia. CT demonstrated capsular-putaminal infarction with modest anterior-superior extension. The absence of aphasia is somewhat surprising, although the profile and CT are not greatly different than our Case 4, who was also no longer aphasic by day 57 of his illness. Finally, Case 2-5 had no aphasia at 79 days after a left putaminal haemorrhage. It is impossible to judge the extent of the lesion because only an enhanced scan (at day 15) was published. In summary, we believe that the findings of this other large investigation of aphasia after capsular-putaminal lesions are very compatible with our model. Minor discrepancies may be based on small differences in CT interpretation which cannot be resolved due to limitations in the number of CT scan sections which were published.



Damasio *et al.* (1982) reported 8 cases of aphasia after capsular-putaminal infarction. The lesions in these cases were smaller than the lesions in our report of the same year (Naeser *et al.*, 1982); some apparent discrepancies in the two reports were correctly attributed to the factor of size. In our present report, many patients had small lesions, and we believe that the discrepancies disappear. Cases 1 and 3–6 in Damasio *et al.* (1982) had dysarthria, nonfluent aphasia and hemiparesis. In Cases 1, 3, 5 and 6 fluency rapidly improved; Case 4, although nonfluent, 'spoke spontaneously' and had 'profuse paraphasia'. Cases 1, 3, 5 and 6 initially had impaired auditory comprehension, but all showed much improvement. Only Case 4 apparently had no improvement in comprehension. This patient had the most inferior lesion (the only case in which published CT scans include a cut below the frontal horns), and at that inferior level had posterior lesion extension perhaps including the TI. We suspect that cases 1, 3, 5 and 6 of Damasio *et al.* (1982) are similar to our Cases 5, 7 and 8 in whom aphasias with dysarthria were also noted. Comprehension defects in our series were mild to moderate and at the functional level of complex material and syntax. The lesion profile in the cases of Damasio *et al.* (1982) was damage to the head of the caudate, ALIC, anterior putamen and superior PVWM, and in Case 1 perhaps anterior-superior PVWM. This, of course, is similar to the CT profile of our cases. In the series of Damasio *et al.* (1982), Case 7 had only dysarthria after a lesion in the medial putamen and the posterior part of the superior PVWM. Case 8 was primarily dysprosodic with a much more lateral putaminal lesion that extended superiorly in the white matter deep to the rolandic cortex for the face. This patient does not pertain to our model. Case 2 of Damasio *et al.* does not fit our model. This patient had normal articulation with fluent, paraphasic language but severely impaired comprehension and repetition. That the patient was fluent is accounted for by the absence of anterior lesion extension. Our model predicts that the Wernicke-like qualities should be associated with lesion in TI which the published scan does not demonstrate. In summary, 6 (or perhaps 6½) of the 7 relevant cases fit our model.

Other reports are of only 1 or 2 cases but are also important. Aram *et al.* (1983) described 2 children with subcortical lesions. Case 1 had a spontaneous intracerebral haemorrhage centred on the left putamen. The child was initially mute with impaired comprehension. Over one month there was change into a profile of nonfluent paraphasic language output apparently without dysarthria and with normal comprehension. CT at that point revealed a low density lesion of the putamen and lateral ALIC with considerable deep frontal anterior extension. The caudate, medial ALIC and GIC were not involved. There was no posterior extension, and while there was superior extension, it strikingly did not involve the PVWM. This scan still demonstrated mass effect so the lesion localization must be considered provisional. Nevertheless, the case is in perfect agreement with our model, even to the absence of dysarthria because of sparing of both the superior PVWM and the posteromedial ALIC/GIC region. That the child showed excellent recovery at six months could be due to the final lesion distribution or to her young



age or to both. Case 2 in this series was simply dysarthric: CT showed an infarct involving the posterior putamen, PLIC, GIC and superior PVWM. This is the same as Case 7 of Damasio *et al.* (1982); it is virtually the exact complement (dysarthria, no aphasia) of Case 1 in Aram *et al.* (1983) (normal articulation, nonfluent aphasia). It is compatible with our model; the dysarthria (without aphasia) is caused by a strategically placed superior PVWM lesion affecting the descending motor systems.

Cambier *et al.* (1979) reported a single case with a spontaneous haemorrhage in the head of the left caudate nucleus. The patient was an elderly woman; language examination was performed from two to six weeks after onset. Language was well-articulated, fluent and nonparaphasic with normal repetition and comprehension. In fact, it is not clear that she was aphasic. Behaviour was very abnormal in all cognitive realms, dominated by perseveration, lack of inhibition or self-critical capacity. In tests of word list generation, there were bizarre perseverations, augmentations and distracted stimulus-bound behaviours. At the initial examination the patient had bilateral grasp reflexes and had been incontinent of urine. CT scan at six days after onset demonstrated a small haemorrhage of the head of the caudate with deep frontal white matter oedema but little mass effect. Without later CT it is impossible to be certain of the exact extent of the lesion. It is compatible with our model that this lesion showed no isolatable aphasia syndrome as there was apparently no lesion extension in any of the critical directions. The authors consider the case to be an example of loss of inhibition of frontal functions, particularly frontal verbal (i.e., left frontal) behaviours. Patients with acute ICH in the putamen or thalamus often go through an early period—at times prolonged—of confusion and attentional disturbance with bizarre perseverative augmented and disinhibited responses (Alexander and LoVerme, 1980). This patient suggests that ICH of the caudate can produce similar behaviours. Other recent large series of caudate haemorrhage did not describe exactly similar behaviours (Stein *et al.*, 1984; Weisberg, 1984), but they provided evidence that confusion is common in this setting. In addition, Stein *et al.* (1984) stated that 1 patient had a global aphasia after 'lobar extension' of haemorrhage in the left frontal lobe; the CT of that case was not published. Choi *et al.* (1983) described 2 cases of left ICH in an attempt to attribute amnesia to medial thalamic haemorrhage. Both cases also had haemorrhage in the head of the left caudate, and both cases had bizarre and perseverative behaviours without explicit aphasia.

Sterzi and Vallar (1978) reported a single case with language impairment after a subcortical lesion. The patient had no overt aphasia; the only language abnormality was a decrease in spontaneous speech, but there was also no spontaneous concern about disease and a 'dull' manner was prominent. There was marked perseveration, but it was not restricted to language. One poorly reproduced CT section was published showing decreased density in the medial putamen, globus pallidus, ALIC, and possibly GIC and anterolateral thalamus. The times postonset for the examination and the CT scan were not given. It is difficult to comment on

this case except to state that the patient was not aphasic, which was compatible with the lesion profile.

Mazzocchi and Vignolo (1979), in the midst of a very lengthy report of CT/aphasia correlations, briefly mentioned 4 patients with relevant subcortical lesions. Three 'acute' (examined within the first 21 days) cases had 'very small infarcts' of capsular-putaminal territory with only 'occasional hesitations and anomias'. No CT scans were published. One 'recent' (examined between days 21 and 60) case had 'a slight dysarthria'. The CT scan showed an infarct of the lateral putamen, lateral ALIC and some anterior-superior PVWM. The caudate, medial ALIC, GIC and most PVWM were not involved. These cases are totally compatible with our observations, at least as predicted on the published scans. In this report, the authors also noted 5 cases of Broca's aphasia and 5 cases of global aphasia with purely subcortical lesions. The 10 published lateral reconstructions and the 2 published CT scans (2 slices each) seem compatible (to our eyes) with our hypotheses, but the definition of Broca's aphasia is too broad and the published subcortical detail too scant to be certain. We have not included these 10 cases in our tabulation.

Wallesch *et al.* (1983) also reported a large group of patients with either white matter or nuclear lesions, but the lesion schematics do not indicate clear differentiation between groups, and the method of evaluation does not allow ready comparison. We do not believe that this study can be used to measure our model.

The case of Barat *et al.* (1981) is distinguished by virtue of a detailed postmortem study. Examination was from the third week after onset until death at eight weeks after onset. There was a right hemiplegia but no dysarthria. Language was fluent and nonparaphasic, but throughout all realms of testing (naming, writing, reading, etc.), there were consistent error types—confusions, perseverations, omissions, bizarre responses and confabulations. There was marked fluctuation in attention and affect. CT findings were not published. Postmortem examination revealed a single infarct, wholly subcortical in its distribution. It involved the head and anterior body of the caudate, the ALIC and most of the putamen. There was some extension into the superior PVWM, and the temporal isthmus. The anterior nucleus of the thalamus was also involved. Like the case of Cambier *et al.* (1979), it is difficult to assess the degree of aphasia. There was a behavioural change which disrupted all cognitive activities, although particularly language. With lesions in both the capsular-putaminal territory and the anterior thalamus, clinical-anatomical correlations are problematic. At best, we can conclude that the absence of any anterior or extra anterior extension accounts for the retained fluency and that it is surprising that articulation was normal with lesions of both the ALIC and superior PVWM.

We are aware of three articles which are not about subcortical aphasia but which contain relevant case reports. In an investigation of the vascular pathology which underlies capsular-striatal infarctions, 4 patients with aphasia were described (Bladin and Berkovic, 1984). Little clinical detail was provided, but CT schematics are adequate to document involvement of the anterior-superior PVWM, anterior

PVWM and superior PVWM in these cases. In another study which investigated the CT correlates of nonfluency (Knopman *et al.*, 1983), one example (Case 84) is noteworthy. This patient was described as persistently nonfluent with the smallest CT lesion in the authors' group of nonfluent aphasics. CT scan (fig. 5, p. 1174) demonstrated a subcortical lesion with moderate anterior and anterior-superior PVWM extension, but an enormous superior PVWM extension. We believe that this is compatible with our cases and the suggested mechanism of subcortical nonfluent aphasia. A recent study of the neurobehavioural consequences of subcortical vascular lesions (Fromm *et al.*, 1985) included 3 patients relevant to our review. Case 1 had a transient confusional state with minimal anomia after a small left caudate haemorrhage without any involvement of ALIC or any PVWM demonstrated. Case 2 had only transient dysarthria after an ICH completely restricted to left putamen; voice volume was not described. Case 5 had severe dysarthria after an infarct in left superior PVWM, exactly as expected. Case 3 was unresponsive after left subcortical infarction, and thus no behavioural data were obtained. Case 4 had an ICH in the left thalamus; we have specifically excluded thalamic cases from our present study.

In conclusion, a review of 61 previously reported cases suggests few incompatibilities with our model. Most apparent exceptions are found in patients with more pervasive behavioural disturbances than simply aphasia. Case 2 of Damasio *et al.* (1982) stands out as the only patient with both an uncomplicated aphasia and an adequate published CT scan in whom there is a discrepancy with our theory.

### Conclusions

Current evidence from aphasia assessment and CT scan lesion studies suggests a coherent relationship between subcortical lesions and language/speech disorders. We have outlined this relationship in a model described above. Small lesions of the striatum and/or lateral ALIC cause no aphasia or, at most, mild word finding difficulty or hesitancy. Even lesions extending from the lateral putamen through the lateral ALIC and head of caudate do not cause more than mild word-finding deficits. When lesions extend beyond that territory, various speech and language disorders occur in predictable relationships to the exact lesion extent, that is, anterior, extra anterior, anterior-superior, superior or posterior PVWM, as well as TI, insular cortex or external capsule, or some combination.

This model suggests that white matter pathways are the critical structures in the language disorders. For some aspects of the disorders, there are grounds to speculate on the pathways involved. We have outlined a hypothesis about the importance for auditory comprehension of the medial geniculate to temporal lobe pathway in temporal isthmus and the auditory association callosal pathway in posterior PVWM. When lesions extend lateral and/or superior to the putamen, the external and extreme capsules and/or the arcuate fasciculus can be involved. There is reasonable evidence for the relevance of damage to these structures to a repetition

disturbance with phonemic paraphasias more marked than in spontaneous speech. Damage to the motor pathways for speech output can involve the superior PVWM and the GIC in which corticobulbar fibres descend. They can also involve the slightly more anterior parts of the superior PVWM and the ALIC in which pathways from the motor association cortex to contralateral cerebellum descend and those from the ventrolateral thalamus to motor cortex ascend. Damage to the anterior-superior PVWM involves the pathways from the supplementary motor area to Broca's area; this injury seems to be the minimal critical lesion for TCMA. Extra damage to deep anterior frontal white matter along the genu of the corpus callosum, especially when combined with anterior-superior and superior PVWM extension, may interrupt all pertinent anterior callosal pathways. No doubt other key systems are involved which contribute to the limitations in speech output after this constellation of lesions. Furthermore, simultaneous involvement of cortical structures and related subcortical structures may produce deficits which would not be expected by simply adding the deficits produced by the lesions individually. There is too little investigation of this question to anticipate effects of multiple lesions.

We believe that there is little evidence that striatal structures themselves are important in the aphasia syndromes. Studies of focal lesions, degenerative disorders (Mayeux *et al.*, 1983) or surgical lesions (Bell, 1968) all provide scant examples of aphasia apart from those cases with dementia. Speech disturbances (dysarthria, hypophonia and accelerated rate) occur with striatal disease (Darley *et al.*, 1975) and so may be at least in part caused by striatal damage in cases of vascular disease. The exact pathophysiology of hypophonia, for instance, is one interesting problem yet to be resolved. Recent reports of positron emission tomography (PET) provide some corroboration for emphasis of the white matter lesions. PET in basal ganglia diseases either shows no cortical (Kuhl *et al.*, 1982) or mild diffuse cortical change (Kuhl *et al.*, 1984). Precisely localized subcortical white matter lesions, on the other hand, may cause considerable decrease in metabolism in cortical areas related to the distribution of the damaged pathways (Kushner *et al.*, 1984). Metter *et al.* (1985) have documented the comparative CT, PET and autopsy findings in a case with bilateral lacunar lesions. On one side (the left), CT showed small infarctions involving the anterior limb of the internal capsule. PET demonstrated frontal convexity hypometabolism, and autopsy confirmed the capsular lacunes and documented structural integrity of frontal cortex. On the other side (the right), CT showed and autopsy confirmed infarction in the putamen; PET was normal in frontal regions. The authors supposed, and we agree, that PET has demonstrated a pathway effect (a disconnection), confirming the importance of lesions of key white matter pathways in the production of functional impairments. We anticipate that the use of higher quality CT, MRI and PET together will further clarify the effects of direct subcortical nuclear damage as well as the distant physiological cortical effects of damage to white matter pathways, alone or in combination. To facilitate this clarification, we suggest that reports of subcortical cases in the future

publish enough scan sections (of whatever technique) that the entire lesion can be viewed.

It should not be concluded that this report argues that there is *no* unaccounted variability in aphasia. There are clear accounts of events such as the dramatic recovery of reading despite total loss of left occipitotemporal and posterior callosal structures (Friedman and Alexander, 1984), and other anomalous phenomena. One of the compelling areas for neuropsychological research is accounting for these deviant cases and, in general, for variability in neurological syndromes and in degree of recovery. Age and maturity of the brain at the time of injury, distribution of cerebral asymmetries, and premorbid language capacity are some of the many factors which may play a role in functional variability and recovery potential. Nevertheless, before playing the variations, the theme must be played. Much of the alleged variability in subcortical aphasias actually represents different syndromes caused by different lesions. As with the relationship of cortical damage to aphasia, there seem to be several robust clinical-anatomical correlations between subcortical structures and aphasia. Our model is a step towards the clinical-anatomical correlations which will establish a theme for subcortical structures and aphasia.

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## APPENDIX

Summary of clinical, CT, speech and language data on all 19 patients. Language scores represent standard scoring of the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1972).

| <i>Case</i> | <i>Age</i> | <i>Lesion</i> | <i>Location</i>                                                                                                                 | <i>Hemiparesis</i>   | <i>Speech</i>                                                |
|-------------|------------|---------------|---------------------------------------------------------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------|
| 1           | 54         | Infarct       | Insula and subjacent white matter (fig. 5)                                                                                      | None                 | Normal                                                       |
| 2           | 53         | Infarct       | Insula and subjacent white matter                                                                                               | None                 | Normal                                                       |
| 3           | 66         | Infarct       | Anterior putamen, anterolateral anterior limb internal capsule (ALIC), small superior periventricular white matter (PVWM)       | Facial; minimal hand | Slight loss of prosody only                                  |
| 4           | 58         | Infarct       | Partial lesion head of caudate, anterior putamen, ALIC, anterior-superior PVWM (fig. 6)                                         | None                 | Normal                                                       |
| 5           | 58         | Infarct       | Head of caudate, extensive putamen, ALIC and genu internal capsule (GIC), and small superior PVWM (fig. 7)                      | Facial; minimal hand | Dysarthria, dysprosody and hypophonia                        |
| 6           | 60         | Infarct       | Anterior-superior PVWM (fig. 8)                                                                                                 | None                 | Questionable hypophonia                                      |
| 7           | 57         | Infarct       | Head of caudate, extensive putamen, large ALIC and anterior, superior and anterior-superior PVWM (fig. 9)                       | Hemiplegia           | Dysarthria, dysprosody                                       |
| 8           | 54         | Infarct       | Same lesion as Case 7                                                                                                           | Hemiplegia           | Same as 7                                                    |
| 9           | 66         | Infarct       | Partial lesion head of caudate, extensive putamen, partial lesion ALIC, partial anterior PVWM, and superior PVWM (fig. 10)      | Hemiplegia           | Hypophonia only                                              |
| 10          | 44         | Infarct       | Head of caudate; extensive putamen, large ALIC and GIC; and anterior, superior, anterior-superior and small extra anterior PVWM | Hemiplegia           | Dysarthria, dysprosody and hypophonia in very limited output |
| 11          | 68         | Infarct       | Same lesion as Case 10 plus TI                                                                                                  | Hemiplegia           | Too limited to rate                                          |
| 12          | 56         | Infarct       | Same lesion as Case 10 plus TI, deep frontal and parietal white matter, and patchy insular and parietal cortex                  | Hemiplegia           | Too limited to rate                                          |
| 13          | 55         | Infarct       | Same lesion as Case 10 plus PLIC, TI, deep parietal white matter, and inferior temporal cortex (fig. 11)                        | Hemiplegia           | Stereotypy only                                              |
| 14          | 69         | Infarct       | Same lesion as Case 10 plus TI, temporal cortex and white matter, including Wernicke's area                                     | Hemiplegia           | Too limited to rate                                          |



| <i>Case</i> | <i>Age</i> | <i>Lesion</i> | <i>Location</i>                                                                          | <i>Hemiparesis</i>                      | <i>Speech</i>   |
|-------------|------------|---------------|------------------------------------------------------------------------------------------|-----------------------------------------|-----------------|
| 15          | 56         | ICH           | Extensive putamen, posterior external capsule, PLIC, TI and posterior PVWM (figs 12, 13) | Hemiplegia                              | Hypophonia      |
| 16          | 57         | ICH           | Same lesion as Case 15                                                                   | Hemiplegia                              | Same as Case 15 |
| 17          | 63         | ICH           | Extensive putamen (fig. 14)                                                              | None                                    | Mild hypophonia |
| 18          | 51         | ICH           | Extensive putamen; late scan demonstrated a small hypodense lesion in the superior PVWM  | Hemiplegia                              | Normal          |
| 19          | 42         | ICH           | Lateral putamen, external/extreme capsule, and insular cortex; posterior PVWM (fig. 15)  | Face; moderate hand and arm involvement | Hypophonia      |

| <i>Case</i> | <i>Phrase<br/>length<br/>(1-7)</i> | <i>Articulatory<br/>agility (1-7)</i> | <i>Grammatical<br/>form (1-7)</i> | <i>Auditory<br/>comprehension<br/>(-2 to +1)</i> | <i>Repetition<br/>(0-16)</i> | <i>Reading<br/>Comprehension<br/>(-2 to +1)</i> |
|-------------|------------------------------------|---------------------------------------|-----------------------------------|--------------------------------------------------|------------------------------|-------------------------------------------------|
| 1           | 7                                  | 7                                     | 7                                 | +1.0                                             | 16                           | +1.0                                            |
| 2           | 7                                  | 7                                     | 7                                 | +1.0                                             | 10                           | +1.0                                            |
| 3           | 7                                  | 7                                     | 7                                 | +1.0                                             | 10                           | +1.0                                            |
| 4           | 7                                  | 7                                     | 7                                 | +1.0                                             | 16                           | +1.0                                            |
| 5           | 7                                  | 1                                     | 5                                 | 0.0                                              | 12                           | 0.0                                             |
| 6           | 5                                  | 7                                     | 7                                 | +1.0                                             | 16                           | +1.0                                            |
| 7           | 5                                  | 1                                     | 5                                 | 0.0                                              | 10                           | -0.75                                           |
| 8           | 6                                  | 2                                     | 6                                 | +0.75                                            | 14                           | +0.5                                            |
| 9           | 6                                  | 6                                     | 5                                 | 0.0                                              | 13                           | -1.0                                            |
| 10          | 1                                  | 1                                     | 1                                 | (2 mos) -1.50<br>(6 mos) 0.0                     | 0                            | -1.0<br>0.0                                     |
| 11          | 1                                  | 1                                     | 1                                 | -2.0                                             | 0                            | -2.0                                            |
| 12          | 1                                  | 1                                     | 1                                 | -1.0                                             | 0                            | -1.0                                            |
| 13          | 1                                  | 1                                     | 1                                 | -1.0                                             | 0                            | -2.0                                            |
| 14          | 1                                  | 1                                     | 1                                 | -2.0                                             | 0                            | -2.0                                            |
| 15          | 7                                  | 6                                     | 7                                 | 0.0                                              | 3                            | -1.0                                            |
| 16          | 7                                  | 6                                     | 7                                 | -1.75                                            | 0                            | -1.75                                           |
| 17          | 7                                  | 5                                     | 7                                 | +1.0                                             | 16                           | +0.5                                            |
| 18          | 7                                  | 6                                     | 7                                 | +1.0                                             | 16                           | +0.5                                            |
| 19          | 6                                  | 6                                     | 6                                 | +0.75                                            | 7                            | +1.0                                            |

# ADULT ONSET HALLERVORDEN-SPATZ DISEASE WITH NEUROFIBRILLARY PATHOLOGY

## A DISCRETE CLINICOPATHOLOGICAL ENTITY

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### SUMMARY

Three adults with progressive cognitive decline and extrapyramidal dysfunction were studied. They were all mentally retarded women without known chromosomal abnormalities, ranging in age at the time of onset from 31 to 42 yrs with an average duration of illness of 6 yrs. Neurological signs were stereotyped and consisted of a unilateral equinovarus foot posture followed by progressive dementia, rigidity and quadriparesis. Identical pathological findings were noted in all cases. There was marked deposition of iron-containing pigments in the globus pallidus and reticulate zone of the substantia nigra. Numerous axonal spheroids were noted in these areas and in the gracile and cuneate nuclei. In addition to these typical changes of Hallervorden-Spatz disease (HSD), abundant neurofibrillary tangles (NFTs) were found within the hippocampus, neocortex, nuclei of basal forebrain, subthalamic nucleus and brainstem reticular formation. Rare Hirano bodies and granulovacuolar degeneration were noted within the hippocampus; neuritic plaques and amyloid deposits were absent. Ultrastructurally the NFTs were mostly paired helical filaments (PHFs) with a diameter of 20 to 25 nm and a half-periodicity of 80 nm. Straight filaments and incompletely twisted forms were also seen. Immunocytochemistry with polyclonal antibodies to PHFs was positive in a distribution identical to that of Bodian-positive NFTs. Biochemical analysis of frozen frontal cortex from 1 case revealed a 94% depletion of the cholinergic marker enzyme choline acetyltransferase. Somatostatin-like immunoreactivity was within normal range. Study of 1 case with laser microprobe mass analysis revealed evidence of aluminium accumulation in tangle-bearing hippocampal neurons. Adjacent tangle-free neurons failed to show comparable accumulations. These findings indicate that adult onset HSD occurring in mentally retarded individuals may represent a distinct clinicopathological entity associated with neurofibrillary pathology without amyloid deposition.

## INTRODUCTION

A major difficulty in the nosology of diseases of the basal ganglia concerns Hallervorden-Spatz disease (HSD). Since the original description of a sibship with progressive rigidity and dementia (Hallervorden and Spatz, 1922), many authors have endeavoured to uphold or deny the clinicopathological specificity of this entity (Wigboldus and Bruyn, 1968). In its typical form HSD affects children and adolescents and is manifested mainly as an extrapyramidal disorder with dementia leading to death in early adulthood. While the disease was originally described as familial, sporadic cases have been reported. The diagnosis depends ultimately on neuropathological examination and requires the presence of excess deposition of iron-containing pigments within the globus pallidus and pars reticularis of the substantia nigra. Essential to the diagnosis is the presence of axonal spheroids in those areas, with the occurrence in some cases of more generalized axonal dystrophy, particularly in younger patients (Jellinger, 1973; Seitelberger and Jellinger, 1977).

Although excess iron deposition in these areas can be seen in a variety of conditions, the added presence of axonal spheroids makes the histopathological picture of HSD distinctive. Nonetheless, attempts at clinicopathological correlation have not been predictable as exemplified by case reports with typical pathology and rather diverse clinical presentations (Dooling *et al.*, 1974). In particular, the rare cases of adult onset HSD, recently reviewed by Jankovic *et al.* (1985), demonstrate the wide range of clinical presentations of a single histopathological entity. We wish to report 3 additional cases of adults with HSD united by a distinct clinical presentation and unique pathological characteristics.

## METHODS

### *Histopathology*

The following stains were used for light microscopy: haematoxylin and eosin (H and E) and luxol fast blue (LFB); Bodian or Bielschowsky stains; Perl's Prussian blue; Congo red.

### *Electron microscopy*

Formalin-fixed tissue obtained at autopsy was postfixed in 3.5% glutaraldehyde, washed in Sabatini's buffer solution, dehydrated in graded alcohols, infiltrated with propylene oxide and Polybed-812, and embedded in Polybed-812. Thin sections were stained with uranyl acetate and lead citrate and examined with a Jeol 100-S electron microscope.

### *Immunocytochemistry*

Rabbit antiserum was raised against fractions rich in paired helical filaments (PHF) derived from the cerebral cortex of patients with Alzheimer's disease and had been previously characterized (Ihara *et al.*, 1983). Formalin-fixed, paraffin-embedded tissue sections were processed for immunocytochemistry according to the method of Sternberger (1979). The sections were deparaffinized, hydrated, and treated for 30 min with 0.3% hydrogen peroxide in absolute methanol. Slides were then washed once (10 min) with 1% (V/V) goat serum in TS buffer (50 mM Tris-HCl, pH 7.6, 145 mM NaCl), covered with 20% (V/V) goat serum in TS buffer, and incubated for 1 h at room temperature.

Slides were then washed and covered with PHF antiserum at a dilution of 1:200 or 1:500 in 1% goat serum/TS buffer. After incubation at 4°C in a moisture chamber overnight, the slides were washed twice and covered with diluted biotinylated antirabbit immunoglobulin (Vector Laboratories, Burlingame, California) for 60 min at room temperature. Following one wash, the sections were incubated with avidin-biotinylated horseradish peroxidase solution (Vector Laboratories) at room temperature for 45 min, then washed twice in 50 mM TS. The sections were next incubated in a freshly separated solution of 25 mg diaminobenzidine dissolved in 50 ml of 50 mM TS, with 20  $\mu$ l of 30% H<sub>2</sub>O<sub>2</sub> added. The reaction was stopped by washing with running water. The slides were dehydrated and coverslips mounted with Permount.

#### *Biochemical and Enzymatic Analysis*

Frontal cortex from Case 3 was frozen at -70°C approximately 15 h after death. Choline acetyltransferase (ChAT) was measured as described elsewhere (Fonnum, 1969; Davies, 1979). In this method, choline is incubated with [<sup>3</sup>H] acetyl-coenzyme A and radioactivity is measured in the acetylcholine formed. Somatostatin-like immunoreactivity (SLI) was measured by radioimmunoassay in a manner previously described (Crystal and Davies, 1982).

#### *Element Analysis*

Element analysis was performed using the laser microprobe mass analyser (LAMMA). A comprehensive description of this technique is presented elsewhere (Perl *et al.*, 1986).

Blocks of the pyramidal layer of the CA1 sector of formalin-fixed hippocampus from Case 1 and deparaffinized hippocampus from Cases 2 and 3 were osmicated and embedded in Spurr's low viscosity medium. Semithin sections (0.3  $\mu$ m) were cut with a diamond knife, mounted on 3 mm copper 300 mesh electron microscope grids, stained with toluidine blue and subjected to LAMMA observation and analysis. Neurons were chosen for analysis if the cell nucleus was present in the plane of section. Each selected neuron was first evaluated by light microscopy for the presence or absence of a neurofibrillary tangle. Multiple-point LAMMA analysis was performed in the nucleus and cytoplasm of each selected neuron, as well as in the adjacent neuropil. Five laser shots were taken in each of these three areas from each selected neuron and the resultant mass spectra were collected and analysed. The height (in mV) of the peaks at mass number 27 (corresponding to aluminium) of 40 laser shots derived from each region was averaged.

## CASE REPORTS AND NEUROPATHOLOGICAL FINDINGS

The clinical features are summarized in Table 1.

### *Case 1*

The patient was a mentally retarded 48-year old woman. She was born in Massachusetts and was the oldest of 3 children. There was no family history of nervous or mental disease and her siblings were normal in adulthood. Apart from a forceps delivery, gestation and birth were normal. When aged 2 yrs she was noted to have seizures which resolved. She was described as mildly retarded and lived at home until aged 16 when she was placed in a state institution. When aged 42 she was felt to be able to live in a sheltered environment and was able to converse in complete sentences and read at third grade level. At about that time she was noticed to have a limp and left-sided rigidity. Over the following two years she developed progressive axial and limb rigidity as well as mental deterioration. She was recommitted to a state institution where neurological examination revealed mutism and severe dementia. There were no spontaneous movements of the face or limbs. The cranial nerves were normal. Motor testing revealed a diffuse increase in tone with hyperextension of the legs and equinovarus posture of the right foot. Reflexes were generally brisk with extensor plantar responses. She was unable to walk but there was no evidence of ataxia; sensory testing was grossly normal. A CT scan showed moderate cerebral atrophy (*see fig. 1*). She was placed on levodopa

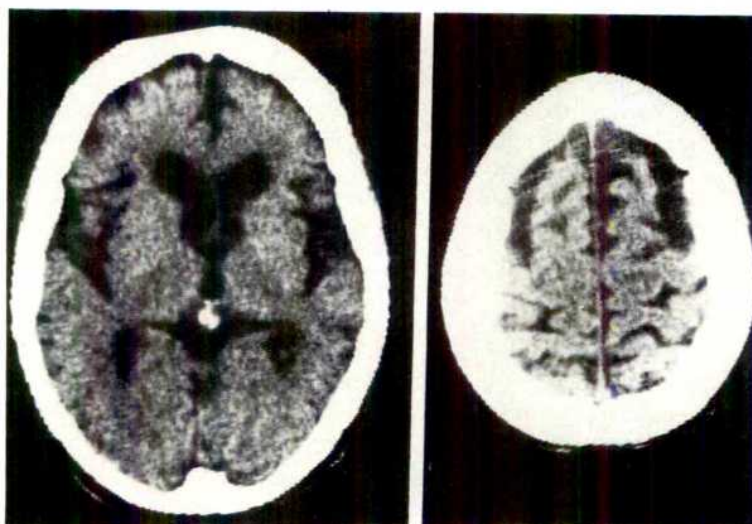


FIG. 1. *Case 1*. CT scan demonstrating marked cortical atrophy and ventricular dilatation. Frontal regions are particularly affected.

without improvement and progressed to a rigid vegetative state with incontinence. She died six years after the initial decline.

*Neuropathological findings.* The brain weighed 1060 g after fixation. There was marked cortical atrophy affecting primarily the frontal lobes. The ventricles were dilated symmetrically. Although the globus pallidus was normal in size it showed bilaterally symmetric rusty discolouration; similar changes were noted in the substantia nigra. The pons, medulla and cerebellum were normal in appearance.

The major histopathological changes are summarized in Table 2. Microscopically there was striking neuronal loss in the neocortex with disappearance of horizontal lamination. With the Bodian stain,

TABLE 1. CLINICAL CHARACTERISTICS

|                             | <i>Case 1</i> | <i>Case 2</i>     | <i>Case 3</i>  |
|-----------------------------|---------------|-------------------|----------------|
| Age at onset (yrs)          | 42            | 32                | 31             |
| Sex                         | F             | F                 | F              |
| Duration (yrs)              | 6             | 10                | 2              |
| Baseline mental retardation | Mild          | Mild/<br>moderate | Severe         |
| Dementia                    | +             | +                 | + <sup>2</sup> |
| Dysarthria/mutism           | +             | +                 | + <sup>2</sup> |
| Focal dystonia              | +             | +                 | +              |
| Rigidity                    | +             | +                 | +              |
| Tremor                      | —             | —                 | —              |
| Hyperreflexia               | +             | —/+ <sup>1</sup>  | +              |
| Extensor plantar            | +             | —/+ <sup>1</sup>  | +              |
| Response to levodopa        | —             | —                 | Not given      |

<sup>1</sup> Initially not evident but developed later in the course of the illness. <sup>2</sup> Patient was profoundly retarded and mute at the onset of the illness.

TABLE 2. PATHOLOGICAL CHARACTERISTICS

|                                      | <i>Case 1</i> | <i>Case 2</i> | <i>Case 3</i> |
|--------------------------------------|---------------|---------------|---------------|
| Cortical atrophy                     | +             | +             | +             |
| Iron pigments                        | +             | +             | +             |
| Axonal spheroids                     | +             | +             | +             |
| Neurofibrillary tangles <sup>1</sup> | +             | +             | +             |
| Granulovacuolar degeneration         | +             | +             | +             |
| Hirano bodies                        | +             | +             | +             |
| Neuritic plaques                     | —             | —             | —             |
| Motor neuron pathology <sup>2</sup>  | NE            | NE            | +             |
| Lewy bodies                          | +             | —             | —             |

<sup>1</sup> See Table 3 for quantitation. <sup>2</sup> See text for description. This refers to the presence of axonal swellings, chromatolysis and cell loss in anterior horn cells. NE = not examined.

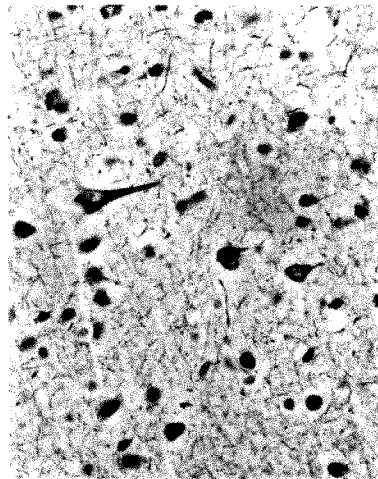


FIG. 2. *Case 1*. Frontal neocortex showing typical Alzheimer neurofibrillary tangles are within pyramidal cells; Bodian stain,  $\times 530$ .

at least a third of the remaining neurons contained neurofibrillary tangles (NFTs) (fig. 2). Neuritic plaques and amyloid deposits in vessel walls were conspicuously absent. Neurofibrillary change was most pronounced in frontal, temporal and parietal association neocortex. Primary sensory and motor cortex was generally spared. The parahippocampal gyrus and hippocampus were also involved, especially the pyramidal cells of Sommer's sector. Immunocytochemistry with polyclonal antibodies to paired helical filaments (PHEs) stained the NFTs in a distribution identical to that of Bodian stain (figs 3A, B). Granulovacuolar degeneration and Hirano bodies were occasionally seen (fig. 4D). Abundant NFTs were noted in the amygdala, mammillary bodies, nucleus basalis of Meynert, nucleus of the diagonal band of Broca, subthalamic nucleus and the pars compacta of the substantia nigra. The topographic distribution of the NFTs is summarized in Table 3.

SNC showed marked neuronal loss with partial or complete depigmentation of remaining neurons; occasional Lewy bodies were noted. Up to a fourth of the remaining neurons contained NFTs. In the substantia nigra, pars reticularis, there was neuronal loss and an abundance of iron-containing pigment was noted around blood vessels and throughout the neuropil. In addition there were

TABLE 3. REGIONAL DISTRIBUTION OF NEUROFIBRILLARY TANGLES<sup>1</sup>

|                               | <i>Case 1</i> | <i>Case 2</i>   | <i>Case 3</i> |                           | <i>Case 1</i> | <i>Case 2</i> | <i>Case 3</i> |
|-------------------------------|---------------|-----------------|---------------|---------------------------|---------------|---------------|---------------|
| Neocortex                     |               |                 |               | Thalamus                  |               |               |               |
| Frontal                       | 2+            | 3+              | 2+            | n. Anterior               | 1+            | 2+            | 1+            |
| Temporal                      | 3+            | 3+              | 2+            | VPL/VPM                   | 0             | NE            | 2+            |
| Parietal                      | 2+            | NE              | 3+            | Subthalamic nucleus       | 2+            | 2+            | 3+            |
| Occipital:                    |               | NE              |               | Midbrain                  |               |               |               |
| Striate                       | 0             |                 | 0             | SNc                       | 1+            | 1+            | 1+            |
| Association                   | 3+            |                 | 2+            | SNr                       | 0             | 0             | 0-1+          |
| Hippocampus and related areas |               |                 |               | Periaqueductal grey       | 1+            | 1+            | 3+            |
| Entorhinal                    | 3+            | 4+ <sup>2</sup> | 4+            | Oculomotor nuclei         | 0             | 0             | 0             |
| Subicular area                | 3+            | 4+              | 4+            | Pons                      |               |               |               |
| CA1                           | 4+            | 4+              | 3+            | Median raphe              | 2+            | 2+            | 3+            |
| CA2                           | 1+            | 2+              | 3+            | Periaqueductal grey       | 2+            | 2+            | 4+            |
| CA3                           | 1+            | 2+              | 1+            | Cranial nerve nuclei      | 0             | 0             | 0             |
| CA4                           | 2+            | 1+              | 1+            | Locus coeruleus           | 2+            | NE            | 2+            |
| Amygdala                      | 1+            | 1+              | 1+            | Medulla                   |               |               |               |
| Mammillary nuclei             | 2+            | 3+              | 3+            | Dorsal motor n. $\bar{X}$ | 1+            | NE            | 1+            |
| Basal forebrain               |               |                 |               | Cerebellum                | 0             | 0             | 0             |
| NBM                           | 3+            | 4+              | 3+            |                           |               |               |               |
| NDB                           | 3+            | 4+              | 4+            |                           |               |               |               |

<sup>1</sup> NFT were quantitated as percentage of tangle-bearing neurons per medium power field. The following ranking system was used: 1+ = 0–20% tangle-bearing neurons per MPF; 2+ = 20–50%/MPF; 3+ = 50–75%/MPF; 4+ = 75–100%/MPF. <sup>2</sup> Underlining (e.g. 4+) signifies marked neuronal loss with NFTs in remaining neurons. NBM = basal nucleus of Meynert; NDB = nucleus of diagonal band; VPL = n. ventralis posterior lateralis; VPM = n. ventralis posterior medialis; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata.

numerous axonal spheroids and diffuse fibrillary astrocytosis. Similar changes were present in the globus pallidus, particularly in the inner segment. The caudate and putamen were slightly reduced in size but did not contain spheroids or NFTs. Occasional NFTs were noted in the thalamus, particularly in the anterior and ventroposterior nuclei; these were also noted in the median raphe, periaqueductal grey matter and the dorsal nucleus of the vagus. The brainstem was otherwise normal apart from the presence of numerous axonal spheroids within the gracile and cuneate nuclei. The spinal cord was not examined.

Ultrastructural examination of the NFTs revealed these to be principally composed of typical PHFs with a diameter of 20–25 nm and a half-periodicity of 80 nm. Straight filaments and incompletely twisted forms were also noted, at times within the same neurons containing PHFs (fig. 4A–C). Hirano bodies were also noted (fig. 4D).

#### Case 2

The patient was a 42-yr-old mentally retarded woman. She was born in Britain and was the first of 2 children. A younger brother was normal. There was no family history of nervous or mental disease; gestation and birth were uncomplicated. Seizures were noted at 2 months and persisted intermittently until the age of 6 yrs. She was developmentally delayed and when aged 12 was placed



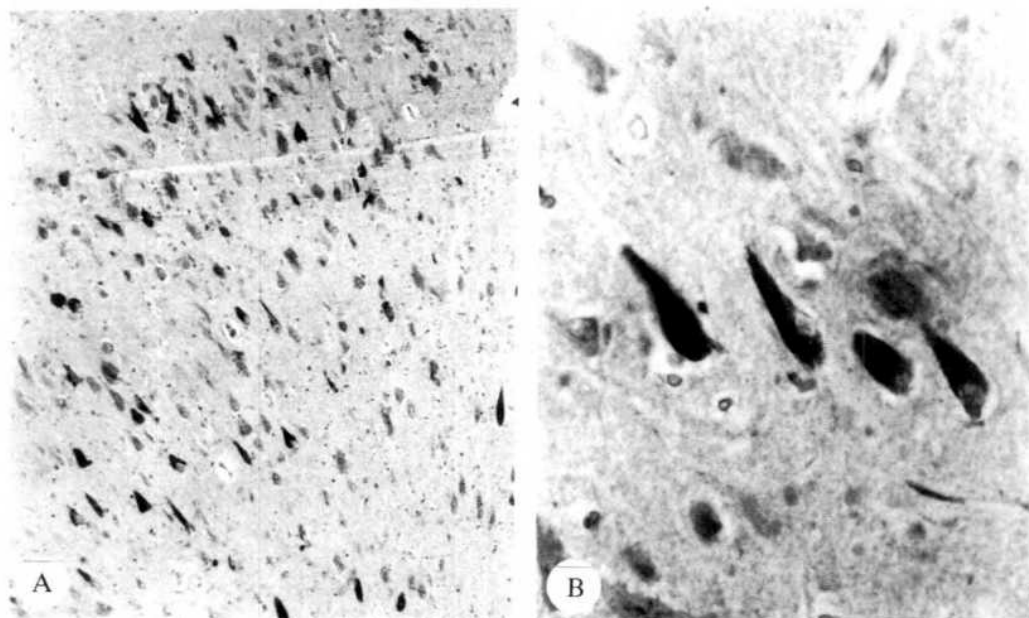


FIG. 3. Case 1. Hippocampus. A, most Bodian-positive pyramidal cells also stain positively with polyclonal antiserum to PHF; PHF immunoperoxidase,  $\times 130$ . B, higher magnification,  $\times 530$ .

in a special school. During adolescence she was described as talkative, interested in her surroundings and an avid walker. When aged 30 she was placed in a vocational training centre. Two years later she became increasingly withdrawn and developed progressive speech difficulties and postural instability. Neurological testing revealed masked facies, marked rigidity of trunk and limbs and an equinovarus posture of the left foot. She was severely dysarthric. Frequent episodes of 'freezing' were noted while walking. Reflexes were generally reduced and the plantar responses flexor. Sensation was grossly preserved. A trial of levodopa and amantadine was of no benefit and in the subsequent four years she progressed to a state of profound dementia with incontinence. Repeat examination when aged 38 revealed a rigid vegetative state with paraplegia in extension and fixed inversion of the left foot. Plantar responses were extensor. She died from pneumonia four years later.

*Neuropathological findings.* The brain weighed 920 g after fixation. There was generalized gyral atrophy in both cerebral hemispheres especially the frontal lobes. The lateral ventricles were symmetrically dilated. There was a light brown discolouration of the globus pallidus. The substantia nigra showed similar bilateral rusty discolouration. The cerebellum and brainstem appeared grossly normal.

Microscopically, the changes conformed to those described in Case 1 and are summarized in Table 2. There was narrowing of the cerebral cortex with marked neuronal loss and fibrillary astrocytosis. Numerous globose and flame-shaped NFTs were evident on Bodian staining and on immunocytochemical staining for PHFs; their topographical distribution is given in Table 3. NFTs were found mostly in the pyramidal cells of frontal, temporal and parietal association neocortex. Primary sensory and motor cortex was generally spared. Particularly pronounced neurofibrillary changes were seen in the parahippocampal gyrus and hippocampus. The latter also showed marked granulovacuolar degeneration and occasional Hirano bodies. There were no amyloid deposits and neuritic plaques were absent. Numerous NFTs were also found in the nucleus basalis, nucleus of the diagonal band, anterior thalamic nucleus, substantia nigra pars compacta, subthalamic nucleus, mamillary bodies

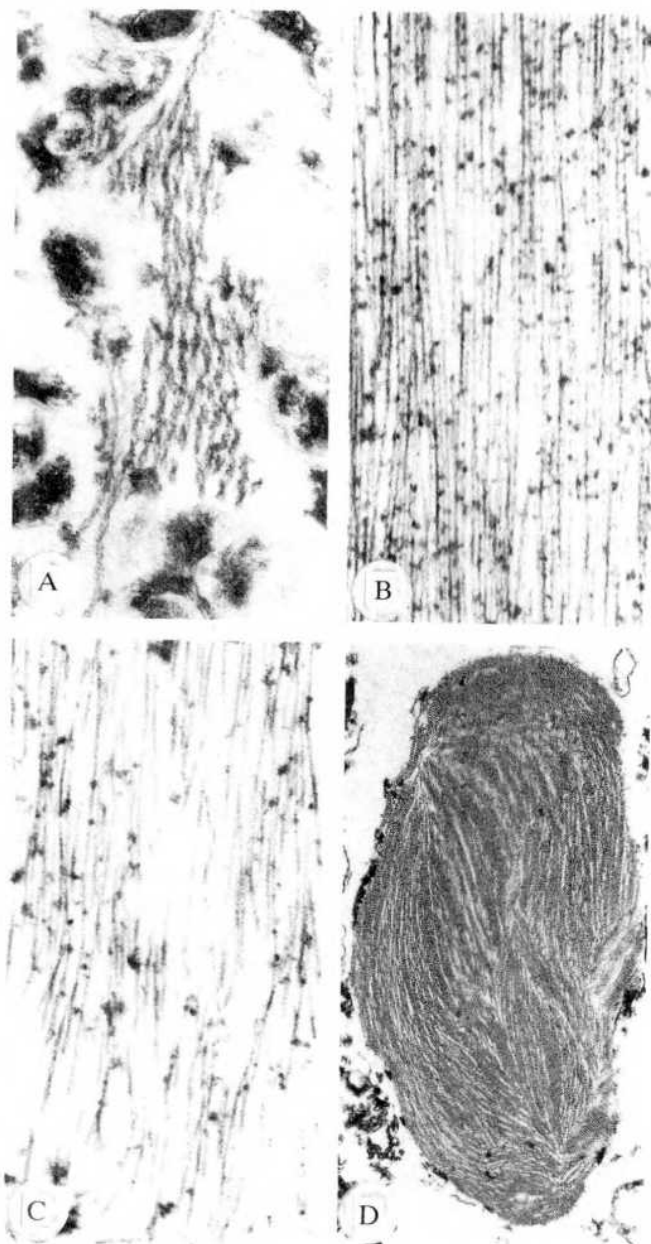


FIG. 4. *Case 1*. Pyramidal cell layer of hippocampus. Electron microscopy. A, typical PHF. B, straight filaments and PHFs within the same neuron. C, bundle of straight filaments. Bar =  $0.5\ \mu\text{m}$ . Bars =  $0.1\ \mu\text{m}$ . D, typical Hirano body.

and periaqueductal grey matter. NFTs reacted strongly with PHF antiserum. Ultrastructurally the tangles contained typical PHFs mixed with occasional straight forms.

Whereas the caudate and putamen were preserved, the pallidum was distinguished by striking neuronal and myelinated fibre loss. On H and E staining the entire background was dominated by the presence of eosinophilic spheroids ranging in size from 5–50  $\mu\text{m}$  faintly reactive with the Bodian stain and PHF antiserum. There were numerous areas of mineralization of both the parenchyma and blood vessels. There was also a moderate amount of granular iron-positive pigment scattered throughout the neuropil. Deposits of lipofuscin-like pigment were present within cell processes.

The substantia nigra was characterized by marked neuronal depletion in the pars compacta with depigmentation of the remaining cells and the presence of NFTs. The pars reticularis and the abutting ventral pars compacta contained frequent axonal spheroids and large amounts of iron-containing pigments identical to those noted in the globus pallidus.

The remainder of the brainstem was normal with the exception of frequent NFTs in periaqueductal grey and the median raphe and the presence of typical axonal spheroids in the gracile and cuneate nuclei and the spinal nucleus and tract of the trigeminal nerve. The spinal cord was not examined.

### Case 3

The patient was a mentally retarded 32-yr-old woman. She was born in Massachusetts and was the last of 3 siblings with 2 normal older brothers and no family history of nervous or mental disease. Gestation and birth were normal but motor milestones were delayed such that she could not walk until 2 yrs of age. Language skills were similarly delayed. A single generalized seizure occurred following an immunization booster at the age of 2 yrs. Although she never acquired speech, she was described as visually attentive and able to execute simple verbal commands. She was placed in a state institution where she functioned at a low level, communicating by grunting and requiring assistance in bathing, dressing and eating. When aged 31 her gait deteriorated and she required assistance to walk. She was noted to have bilaterally pronated feet with an equinovarus posture of the left foot. By the following year she was unable to stand unassisted.

Examination revealed a spastic quadriparesis in extension with hyperreflexia and fixed inversion also of the right foot; the plantar responses were extensor. She became confined to bed and died suddenly one year later.

*Neuropathological findings.* The brain after fixation weighed 1135 g. There was mild cortical atrophy affecting particularly frontal lobes. The globus pallidus and substantia nigra showed a similar rusty brown discolouration. The other deep nuclei, pons, medulla and cerebellum were normal in appearance.

Microscopically the changes were similar to those noted in the preceding cases (see Table 2). There was marked neuronal loss and neurofibrillary change in a distribution identical to that in the above cases (see Table 3). Amyloid deposits and plaques were absent.

As in the other cases, large amounts of iron-containing pigment and numerous axonal spheroids were present throughout the pars reticularis of the substantia nigra and the globus pallidus (fig. 5A, B). Of note was a more generalized scattering of axonal spheroids involving most cortical fields and the thalamus. Juxtaneuronal axonal swellings were detectable in the third and fourth nerve nuclei including the Edinger-Westphal nucleus, the spinal nucleus and tract of the fifth nerve, the lateral vestibular nucleus and the gracile and cuneate nuclei. Occasional axonal swellings were noted within cerebellar cortex (torpedoes) as well as the subcortical white matter.

In the spinal cord the anterior horns at all levels showed moderate to marked neuronal loss and fibrillar astrocytosis. Some remaining neurons showed active degenerative change characterized by a loss of Nissl substance, ballooning of the cell body with occasional vacuolation of the cytoplasm

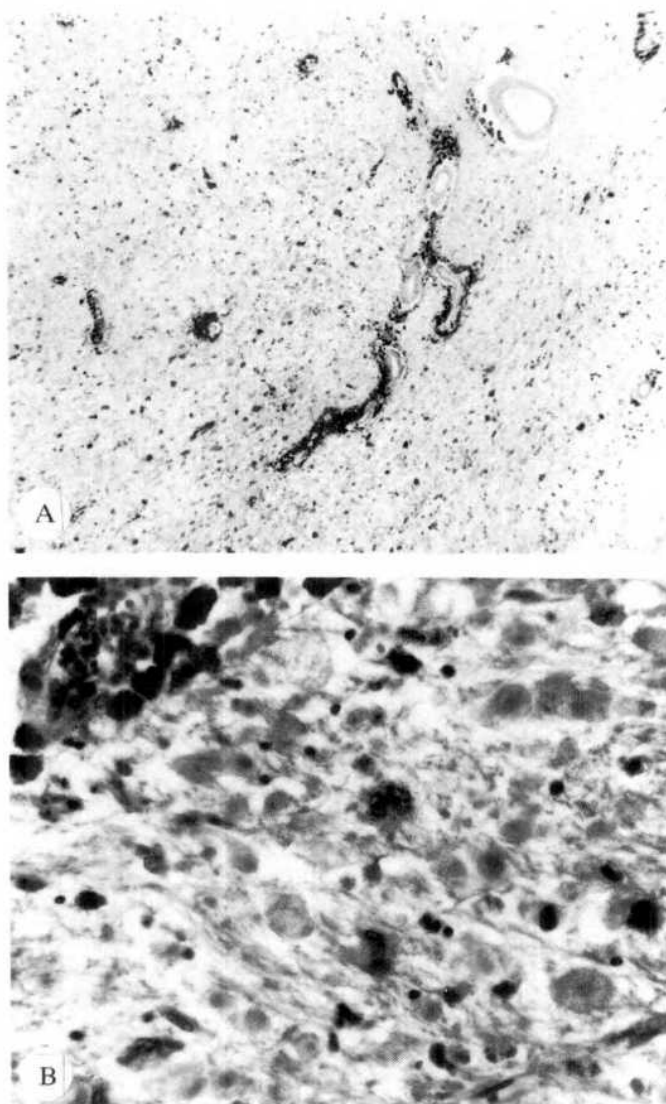


FIG. 5. *Case 3.* Pars reticularis of substantia nigra. A, perivascular and parenchymal deposits of iron-containing pigments; Prussian Blue stain,  $\times 52$ . B, higher magnification showing anoxal spheroids and perivascular accumulation of pigment; H and E, LFB,  $\times 530$ .

and peripheral displacement of the nucleus (fig. 6). In addition, a large number of irregularly shaped pale eosinophilic bodies and axonal swellings were noted throughout the anterior horns as well as in Clarke's column. The corticospinal tracts showed some myelin loss with fibrillar astrocytosis; the spinocerebellar tracts were similarly involved but to a lesser degree. Chromatolytic change and neuronal loss were noted to varying degrees in the motor nuclei of the cranial nerves III, IV, V and XII.

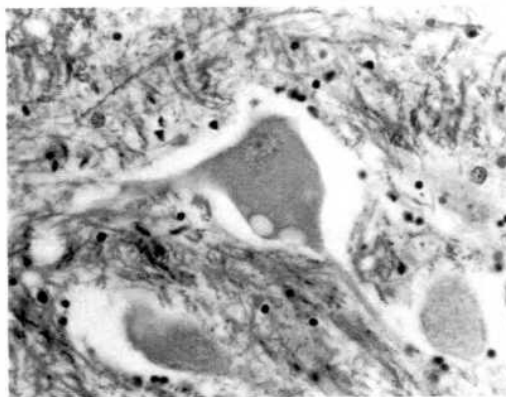


FIG. 6. Case 3. Lumbar spinal cord. Anterior horn cell undergoing chromatolysis with ballooning of cell body and vacuolation of cytoplasm; H and E, LFB,  $\times 530$ .

TABLE 4. CHOLINE ACETYLTRANSFERASE (ChAT) AND SOMATOSTATIN-LIKE IMMUNOREACTIVITY (SLI) IN FRONTAL CORTEX

|                                           | ChAT <sup>1</sup> | SLI <sup>2</sup> |
|-------------------------------------------|-------------------|------------------|
| HSD with neurofibrillary tangles (Case 3) | 32                | 2.14             |
| Alzheimer's disease controls              | 59 $\pm$ 35       | 0.73 $\pm$ 0.15  |
| n                                         | 14                | 12               |
| Mean age (yrs)                            | 61 $\pm$ 7        | 74 $\pm$ 8       |
| Normal controls                           | 531 $\pm$ 91      | 2.95 $\pm$ 0.41  |
| n                                         | 12                | 12               |
| Mean age (yrs)                            | 57.2 $\pm$ 5.6    | 74 $\pm$ 10      |

<sup>1</sup> ChAT activity is expressed as nmol acetylcholine formed/h/100 mg protein. <sup>2</sup> SLI is expressed as ng/mg protein.

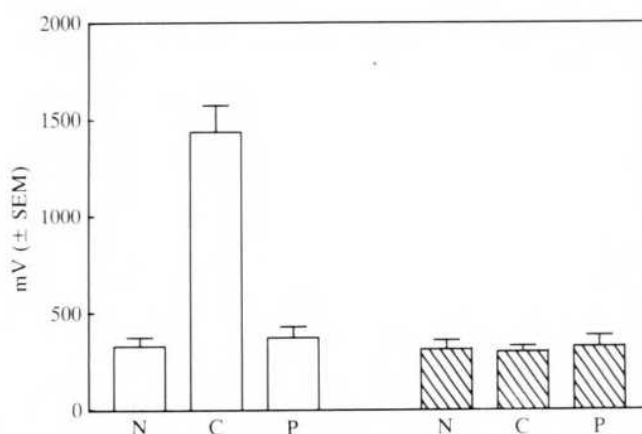


FIG. 7. Case 1. Results of laser microprobe mass analysis of hippocampal neurons. Large aluminium-related peaks are detectable in tangle-bearing neurons (open columns). Comparable peaks were not found in adjacent tangle-free neurons (cross-hatched columns). N = nucleus; C = cytoplasm; P = adjacent neuropil.

## NEUROCHEMICAL FINDINGS

*Biochemical and Enzymatic Analysis*

The findings from Case 3 are summarized in Table 4. Choline acetyltransferase (ChAT) was reduced to 6% of normal control values, but was within range for controls with Alzheimer's disease (AD). Somatostatin-like immunoreactivity (SLI) was within the normal range. SLI from the frontal cortex of AD measured concurrently was reduced to 24% of control values.

*Element Analysis*

LAMMA revealed large aluminium related peaks (mass number 27) in tangle-bearing hippocampus neurons from Case 1 (fig. 7). Adjacent tangle-free neurons did not show comparable peaks. Qualitative comparison revealed equivalently large peaks in hippocampal tangle-bearing neurons from cases of Guamanian ALS (Perl *et al.*, 1986). Aluminium-related peaks were not obtained in the medial globus pallidus, although iron was demonstrated by an x-ray dispersive spectroscopic method. Hippocampal sections from Cases 2 and 3 failed to show aluminium-related peaks. This may have been the consequence of differences in tissue preparations as these were embedded in paraffin for long periods of time before element analysis.

## DISCUSSION

*Clinical Considerations*

We describe 3 patients, all mentally retarded women, who developed a syndrome of cognitive decline and motor dysfunction. The clinical characteristics of these patients are summarized in Table 1. They ranged in age at the time of onset from 31 to 42 yrs with an average duration of illness of 6 yrs. Although the baseline degree of cognitive impairment varied between the patients, all were thought to be stable by their supervisors before the onset of symptoms. In no instance was there a family history of neurological disease and the surviving siblings of the patients were found to be normal in adulthood. Chromosomal analysis was not performed but review of the patients' photographs failed to disclose obvious external dysmorphism, especially of the type seen in Down's syndrome. The clinical cause of retardation was uncertain in each case; in none was there a history of neonatal asphyxia.

In each case there was a relatively abrupt cognitive decline resulting in the loss of interactive skills and requiring a change in the level of supporting care. This was most evident in the first patient who was recommitted to a state institution after a six-year sojourn in the community. The third patient was so impaired at baseline that the mental change was evident only to her supervisors. Gait decline was evident in each patient roughly in parallel with the mental change. All patients demonstrated focal dystonia at onset manifested by equinovarus posture followed by an inexorable progression to generalized axial and limb rigidity and paraplegia in extension. The tendon reflexes varied in the course of the illness, perhaps due to

superimposed rigidity, but the plantar responses inevitably became extensor. Vision and sensation were generally spared but could not be assessed with certainty during the later course of the illness. In no instance was there significant ataxia or visible muscle wasting. Two patients were tried on levodopa and one on amantidine without benefit. A CT scan was performed in 1 patient and showed generalized atrophy. The EEG in 2 patients showed only disorganization of the background activity.

By virtue of the fact that all 3 patients showed pathological changes consistent with HSD, we reviewed existing verified cases with attention to (1) adult onset, (2) preexisting mental impairment, and (3) the presence of neurofibrillary pathology.

Of the adult onset cases cited by Jankovic *et al.*, (1985), only the first case of Onari (1925) involved a preexisting state of mental retardation. This case however, and similarly those of Eicke (1940) and Wahlström (1946), lack the necessary histopathological criteria for designation as HSD and should not be adduced as examples of this disease occurring in adulthood (Wigboldus and Bruyn, 1968; Seitelberger and Jellinger, 1977). Irrespective of nosology, neurofibrillary changes were universally absent.

Several verified cases of HSD have been reported with neurofibrillary pathology. Wisniewski *et al.* (1979) reported two rather typical cases of HSD in children in whom NFTs were noted in the hippocampus. Hartmann *et al.* (1983) reported a 45-yr-old woman with progressive mental decline beginning at the age of 18 yrs. Although the pallidum was discoloured, the authors concentrated on the axonal spheroids and labelled this a case of neuroaxonal dystrophy. NFTs and granulo-vacuolar degeneration were noted in the hippocampus as well as possible neuritic plaques. The patient was found to have additional changes consistent with ALS and pontocerebellar degeneration. Of importance is Shiraki's report (1966) of 2 cases of parkinsonism and dementia (PD) from the island of Guam in whom typical changes of HSD were noted. In addition to widespread NFTs in a distribution similar to our cases, these individuals had a striking deposition of iron-containing pigment and axonal spheroids within the globus pallidus and the pars reticularis of the substantia nigra. One patient was a 40-yr-old Chamorro who had had ALS for 15 yrs and then developed marked mental deterioration; the other was a 61-yr-old Chamorro with a 3-yr history of parkinsonism and dementia. Although only these 2 were individually reported, Hirano noted that pigmentary changes were evident in pallidum and substantia nigra in roughly a third of PD cases and occasionally in ALS cases (Hirano, 1966; Hirano *et al.*, 1966).

In summary, the possible occurrence of HSD among mentally retarded adults has been mentioned sporadically in the literature with variable histopathological correlates. The rather stereotyped clinical course in our patients, as well as possibly several others in the literature, points to a distinctive subgroup within the cohort of patients originally designated by Dooling *et al.* (1974) as clinically atypical cases with typical pathology (group III). The coexistence of neurofibrillary pathology in our patients is unusual and suggests an additional histopathological distinctiveness.

### *Pathological Considerations*

The major pathological characteristics of our patients have been summarized in Tables 2 and 3. Certain features require emphasis. First, although the NFTs were ultrastructurally and immunocytochemically identical to those found in AD, their mere presence is not specific and has been noted in a variety of neuropathological situations (Wisniewski *et al.*, 1970, 1979).

The coexistence of typical PHFs with straight filaments and incompletely twisted forms is also not unusual and has been noted in AD (Selkoe, 1984) and Guamanian PD (Hirano *et al.*, 1968). The absence of neuritic plaques and amyloid deposits serves to distinguish this entity from AD and normal senescence. Moreover, each of our cases displayed abundant NFTs in regions rarely involved in ageing and AD: the subthalamic nucleus, pars reticularis of the substantia nigra, and periaqueductal grey (Ishino and Otsuki, 1975*a,b*; Kemper, 1984). Thus the distribution of NFTs in our material extends beyond that reported in AD and conforms roughly to the distribution reported by Hirano in cases of Guamanian PD (Hirano *et al.*, 1961; Nakano and Hirano, 1983). The presence of granulovacuolar degeneration and Hirano bodies in Sommer's sector of the hippocampus is also not specific and may occur in ageing, AD and Guamanian PD complex. Lewy bodies likewise are not specific although they are typically associated with idiopathic parkinsonism. They have also been described previously in the pigmented brainstem nuclei of patients with HSD (Jellinger, 1973; Dooling *et al.*, 1974), AD, and in the course of normal ageing (Kemper, 1984). In summary, the neurofibrillary and related pathologies seen in these patients are not specific and, for the above reasons, should not be equated with AD or an exaggeration of normal ageing.

The spinal cord was available for examination only in a single case and the results were striking. In addition to the consistent changes of HSD and neurofibrillary pathology described in the other cases, there was marked involvement of anterior horn cells, Clarke's column, the corticospinal tract and the spinocerebellar tracts. The major cytological change was chromatolysis with degeneration and loss of neurons, most pronounced in the anterior horns. This change was found at every level of the spinal cord and extended to involve motor cranial nerve nuclei including the oculomotor system. Central chromatolysis and proximal axonal swelling of anterior horn cells is encountered occasionally in ALS, especially in those with rapid progression (Carpenter, 1968; Chou *et al.*, 1970; Hirano, 1982). With the additional degeneration of the corticospinal tracts, there is evidence in our material of a certain overlap with motor neuron disease. While ALS-like changes have been reported in association with HSD in the United States (Hartmann *et al.*, 1983), Guam (Shiraki, 1966) and the Netherlands (Bots and Staal, 1973), it must be emphasized that the spinal pathology was not limited to motor neurons and that other cell groups and tracts were involved. In addition, this case showed a wider distribution of axonal spheroids than the other 2, diffusely involving the cerebral cortex, brainstem and cerebellar white matter and granule cell layer. Such wide-



spread changes, including the presence of pale eosinophilic bodies within the anterior horns, have been described in cases of infantile NAD (Hedley-Whyte *et al.*, 1968) and in intermediate-onset cases of HSD (Gilman and Barrett, 1973) and suggest a nosological overlap between the two entities. It is conceivable that this patient's profound baseline retardation was related to more global histopathological changes found in the cerebral hemispheres.

### *Neurochemical Considerations*

Analysis of frozen frontal lobe from Case 3 revealed a striking deficit in ChAT, a presynaptic cholinergic marker enzyme, with a concurrent preservation of SLI in the same tissue. A cholinergic deficit was expected by virtue of extensive cell loss and neurofibrillary change within the basal forebrain (Mesulam and Mufson, 1984). Similar neurochemical deficits have been described in AD (Davies, 1979), PSP (Ruberg *et al.*, 1985), and Parkinson's disease (Ruberg *et al.*, 1982) and may account for some of the mental changes in these entities as well as in our patients. Typical HSD without NFTs is not associated with a significant cholinergic deficit (Perry *et al.*, 1985) and is therefore neurochemically distinct from the cases described here. It is conceivable that the cholinergic deficit contributed to the mental retardation which preceded the clinical decline in these patients, although antecedent retardation has been noted in some cases without NFTs with presumably normal cholinergic function.

The preservation of somatostatin immunoreactivity is significant. SLI is normally highest in cingulate, temporal and frontal neocortex and is regionally depleted in AD (Beal *et al.*, 1985) perhaps in parallel with the development of neuritic plaques (Morrison *et al.*, 1985). Our data would suggest that in the absence of plaque formation, somatostatin activity is indeed preserved but more extensive regional sampling is necessary before a definite statement can be made.

### *Aetiological Considerations*

We describe a distinct clinicopathological entity consisting of a distinctive array of neurological and histopathological features, each of varying causation and aetiological significance. Axonal dystrophy and nigropallidal hyperpigmentation have been described in a variety of conditions alone and in combination (Seitelberger and Jellinger, 1977). In an attenuated form similar changes may be an accompaniment of ageing in both humans (Jellinger, 1973) and primates (Bronson and Schoene, 1980); when intensified, these changes are often designated as HSD. Several experimental systems have been developed for the production of axonal dystrophy, the most prominent being chronic vitamin E deficiency in weanling rats. The mode of pathogenesis seems to be excess free radical concentrations in the absence of the antioxidant function of alpha-tocopherol (Jellinger, 1973). It is further postulated that large synaptic terminals of the sort found in the globus pallidus, the pars reticularis of the substantia nigra and the gracile nucleus are particularly vulnerable to these changes but that other classes of axonal terminals

are also susceptible (Hedley-Whyte *et al.*, 1968). The medial segment of the globus pallidus and substantia nigra, pars reticularis, constitute a discrete morphological and physiological unit (DeLong and Georgopoulos, 1979) and normally contain elemental iron in concentrations two to five times higher than the rest of the brain (Szanto and Gallyas, 1966; Vakili *et al.*, 1977). It is known that ferrous iron catalyzes the peroxidation of microsomal lipids *in vitro* and can function as a generator of free radicals (Searle and Willson, 1983), an effect inhibited by pre-treatment with alpha-tocopherol (Triggs and Willmore, 1984). It is thought that an intensification of this effect gives rise to the excess production of free radicals particularly in regions natively rich in iron and perhaps locally depleted of cysteine dioxygenase (Perry *et al.*, 1985). The end result is the generation of axonal spheroids, the deposition of cysteine-bound iron chelates and the ectopic formation of neuromelanin from lipofuscin, these comprising the cardinal morphological changes of HSD (Swaiman *et al.*, 1983; Barden, 1969; Park *et al.*, 1975).

Neurofibrillary degeneration is a well-recognized concomitant of ageing, AD, and a variety of other conditions (Wisniewski *et al.*, 1979; Kemper, 1984). Of the experimental models for the production of NFTs, aluminium is the best known and, at the same time, the most controversial (Selkoe and Kosik, 1984). Although this model, which involves the injection of aluminium salts into the brain or subarachnoid space of rabbits (Wisniewski *et al.*, 1980) is well established experimentally, the tangles produced are ultrastructurally and biochemically quite different from the typical PHFs found in most human neurofibrillary pathologies (Terry and Peña, 1965; Selkoe *et al.*, 1979). Nonetheless, the demonstration of aluminium accumulations within tangle-bearing neurons by x-ray energy dispersion spectrometry and LAMMA, raises the possibility of a relationship between this metallic cation and the pathogenesis of certain human neurofibrillary diseases, particularly AD (Perl and Brody, 1980; Perl *et al.*, 1985) and Guamanian ALS/PD (Perl *et al.*, 1982). Similarly, experimental aluminium-induced neurofibrillary lesions show a reduction in ChAT analogous to that found in AD and in our patient (Kosik *et al.*, 1983). Whether aluminium is indeed aetiological in human disease is not known.

The spinal pathology described in the third patient consisted mainly of axonal swelling, chromatolysis and ballooning of cell bodies within the anterior horns. Several brainstem motor nuclei were similarly affected. Such changes have been described in patients with ALS, especially of short duration, and have been produced in experimental animals by a variety of methods (Price *et al.*, 1984), most notably by the intrathecal introduction of aluminium salts (Troncoso *et al.*, 1982). As with NFT, extrapolation to human disease from animal models is not always warranted. Nonetheless, the demonstration of increased aluminium concentrations in the nuclei of lumbar anterior horn cells amongst Japanese patients with ALS (Yanagihara, 1982) suggests the possibility of such a relationship, whether causal or not is not known.

Thus many of the distinctive neuropathological changes found in our patients

have been produced experimentally by heavy metals, particularly iron and aluminium. Although the relationship of these agents to specific human disease is unclear, it is remarkable that the identical histopathological constellation has been reported amongst Chamorro ALS/PD patients from the island of Guam.

Recent epidemiological study has shown that Guamanian ALS/PD is likely to have been caused by a specific exogenous factor (Kurland and Molgaard, 1982). It has been suggested, based on the investigation of high incidence foci in the Western Pacific, that high water and soil aluminium content and low concentrations of calcium and magnesium may be causative, rather than hereditary factors (Gajdusek, 1982). With changes in irrigation techniques and urbanization, the incidence of this disease has declined rapidly (Garruto *et al.*, 1985). While a similar environmental cause is unlikely in our patients, an intrinsic metabolic defect, perhaps related to the use and transport of heavy metals, may have been present. Alternatively, as in the case of Down's syndrome, other genetic derangements, perhaps involving defective axonal transport of neurofilaments, may play a role in the pathogenesis of the neuronal changes (Gajdusek, 1985).

For now it suffices to regard HSD with neurofibrillary pathology as a distinct clinicopathological entity with implications for the study of other neurodegenerative disorders. Further investigation, including biochemical studies on frozen tissue, is required before a firm statement can be made about aetiology. Although distinctive, the designation of this illness as a discrete disease entity awaits the identification of additional cases.

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# HYPEREXCITABILITY OF CUTANEOUS AFFERENTS DURING THE SUPERNORMAL PERIOD

## RELEVANCE TO PARAESTHESIAE

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### SUMMARY

The excitability of cutaneous afferents in the median nerve of 20 normal human subjects was investigated using a supramaximal conditioning stimulus and a submaximal test stimulus that produced an afferent volley of 20 to 40% of maximum. The intensity of the test stimuli was 1.1 to 1.25 times threshold for the first recruited axons (defined as a compound action potential of approximately  $0.5 \mu\text{V}$ ). The amplitude of the test volley did not reach the control amplitude until conditioning-test intervals of 3.4 ms. This was followed by a period of increased axonal excitability which reached a peak at intervals of 5 to 8 ms and declined gradually into a late phase of subnormality at 15 to 20 ms. The amplitude of the submaximal test potential was potentiated by, on average, 47% (range 9–146%) during the supernormal period. There were no significant changes in latency. The time course and the degree of potentiation were reproducible in the same subject on separate occasions. When the limb was cooled, the latency of the onset of supernormality was increased and the degree of supernormality was decreased and ultimately abolished. There was an inverse relationship between the degree of potentiation and the size of the test volley. High-frequency repetitive stimulation of the digital nerves for 10 min modified axonal excitability and produced spontaneous paraesthesiae that lasted for 20 min after the stimulation. Following this prolonged stimulus train, single submaximal stimuli evoked larger cutaneous afferent potentials than before the train, and the extent of the potentiation during the supernormal period was increased. It is concluded that prolonged repetitive stimulation of cutaneous afferents has two effects, one on axonal threshold, the second on the supernormal period. It is suggested that, in this experimental model, paraesthesiae result from ectopic impulses generated when axonal excitability is highest, namely at the peak of the supernormal period.

### INTRODUCTION

In patients with peripheral nerve disorders, 'positive' symptoms such as pain, paraesthesiae and dysaesthesiae often result from ectopic impulse generation in cutaneous afferents (Lance *et al.*, 1979; Ochoa and Torebjörk, 1980; Nyström and Hagbarth, 1981; Ochoa *et al.*, 1982; Nordin *et al.*, 1984; for reviews, see Culp and Ochoa, 1982; Hagbarth *et al.*, 1984; Rasminsky, 1984). In such patients con-



ventional nerve conduction studies may provide only limited insight into pathophysiology (Burke, 1985; Hagbarth, 1987). Nerve conduction studies can detect deficits in nerve function that are usually responsible for 'negative' symptoms, such as hypaesthesia, weakness and wasting. To document the neural hyperexcitability responsible for 'positive' symptoms requires a different diagnostic approach to nerve function.

After it discharges, an axon undergoes a reproducible sequence of changes in excitability before it stabilizes (e.g., Gasser and Erlanger, 1930; Gasser and Grundfest, 1936; Graham and Lorente de Nó, 1938; Barrett and Barrett, 1982). During the absolute refractory period, the axon is completely inexcitable for 0.5 to 1 ms, dependent on fibre size. There is then gradual recovery to the prestimulus excitability such that the axon can be excited but only by a stronger stimulus (the relative refractory period). The axon then passes into a prolonged phase of hyperexcitability, the supernormal period, during which it is more easily excited, and finally into a second phase of subnormality. If ectopic impulse generation underlies positive symptoms such as paraesthesiae (*see* above references), such impulses will be generated more easily during the supernormal period, when the threshold for excitation is lowest. The passage of an action potential, whether set up by a physiological stimulus or not, might then induce a self-perpetuating axonal discharge.

The refractory period of afferent axons has been the subject of many studies in man, both in normal subjects and in patients with peripheral nerve disorders, and such tests are now standard diagnostic procedures. By contrast, the supernormal period of afferent axons has received relatively little attention (Gilliatt and Willison, 1963; Hopf *et al.*, 1976; Stöhr, 1981*a,b*; Stöhr *et al.*, 1981), and the diagnostic value of such tests has yet to be established. The present study was undertaken to examine in normal subjects the supernormal period of cutaneous afferents in the median nerve, and to relate the findings to microneurographic studies that have demonstrated ectopic impulse generation as the basis of paraesthesiae and dysaesthesiae in some specific disorders of peripheral nerve (Lance *et al.*, 1979; Ochoa and Torebjörk, 1980; Nyström and Hagbarth, 1981; Ochoa *et al.*, 1982; Nordin *et al.*, 1984). A preliminary report of the results was presented to the Australian Association of Neurologists (Ng *et al.*, 1985).

## METHODS

Experiments were performed with informed consent on 20 healthy volunteers of both sexes, aged 19–40 years. A number of subjects, including the authors were studied on multiple occasions to determine the reproducibility of the results and to study a number of factors that might affect the supernormal period.

The skin at the recording and stimulating sites was gently abraded before application of electrodes. the digital nerves of the index finger were stimulated using ring electrodes, and the evoked compound action potential was recorded by surface electrodes at the wrist in a 'monopolar' configuration, with the active electrode over the median nerve and the reference 3–4 cm laterally over the ulnar border

of the wrist. At each conditioning-test interval (*see later*), 16 conditioned and 16 unconditioned responses were averaged, using two stores, each of 512 bins, and a sampling rate dependent on the conditioning-test interval. These were, for averaging sweeps of 10 ms, 20 ms and 30 ms, sampling rates of 51 kHz, 25 kHz and 17 kHz, respectively. Throughout each experiment, skin temperature was monitored using a thermocouple at two sites, adjacent to the stimulating cathode and adjacent to the active recording electrode. If necessary, the limb was warmed using a hair-dryer and then wrapped in blankets. These measures were sufficient to maintain skin temperature at  $32 \pm 2^\circ\text{C}$  throughout the experiment.

The conditioning stimulus consisted of supramaximal pulses of 0.2 ms duration delivered from a constant-voltage source. To minimize stimulus artefact, the duration of the test stimulus was 0.05–0.1 ms. The intensity of the test stimulus was adjusted, routinely, to give a compound sensory action potential, the amplitude of which was 20–40% maximal. The intensity of the stimulus was also defined by reference to the level required to produce a detectable compound sensory action potential, arbitrarily set at  $0.5\ \mu\text{V}$ . The test stimuli used in the present study were thus 1.1–1.25 times this threshold (i.e., 1.1–1.25 T). A maximal potential was usually recorded at 2–2.5 T, and the conditioning stimulus was set 20–50% higher than this.

The interval between the (supramaximal) conditioning stimulus and the (submaximal) test stimulus was varied systematically in steps of 1 ms from 1–10 ms, and then in steps of 2 to 3 ms up to 25 ms. At each interval, the responses to the test stimulus were recorded when conditioned and when unconditioned by the supramaximal stimulus. Measurements were obtained of the latencies and amplitudes of the maximal afferent volley (evoked by the conditioning stimulus) and of the test afferent volley (evoked by the test stimulus). The recorded compound action potential was biphasic (*see* figs 1, 8). Latencies were measured to the onset of the negative phase. Amplitudes were measured peak to peak. The latency and amplitude of the maximal afferent volley provided additional evidence that temperature did not fluctuate and that the recording and stimulating conditions remained constant. In addition, at each interval, the conditioned volley was compared with its own control rather than to a single control value set at the beginning or end of the experiment, so that the effects of small but systematic variations in the test potential could be eliminated.

In 12 experiments, the digital nerves of the index or middle fingers were stimulated at 200 Hz for 10 min using strong but submaximal stimuli in order to produce paraesthesiae in the digit after cessation of the stimulus train (*see* Ochoa and Torebjörk, 1983; Hagbarth *et al.*, 1984). In different experiments, either (1) posttetanic excitability was checked using single stimuli of constant intensity, (2) afferent excitability during the supernormal period was documented for the 5 ms or 6 ms conditioning-test interval, or (3) the time course of the supernormal period was measured. In 5 experiments, a constant-voltage source was used but stimulus current was monitored to control for possible changes in skin resistance. The remaining experiments were performed using a constant-current source (Grass S88 Stimulator with stimulus isolation units and constant current units).

For each stimulus interval, the changes in amplitude and latency of the conditioned-test potential were expressed as a percentage of the values for the unconditioned-test potential.

## RESULTS

### *Refractory Periods*

In all 20 subjects, a test stimulus failed to produce a detectable compound sensory action potential at the 1 ms conditioning-test interval; in 8 subjects it also failed to do so at the 2 ms interval. When the low-threshold axons in the test volley were relatively refractory, the latency of the test potential was increased and its amplitude was reduced (figs 1A, 2), much as occurs with supramaximal test stimuli (Buchthal and Rosenfalck, 1966; Tackmann and Lehmann, 1974). The increase in latency at

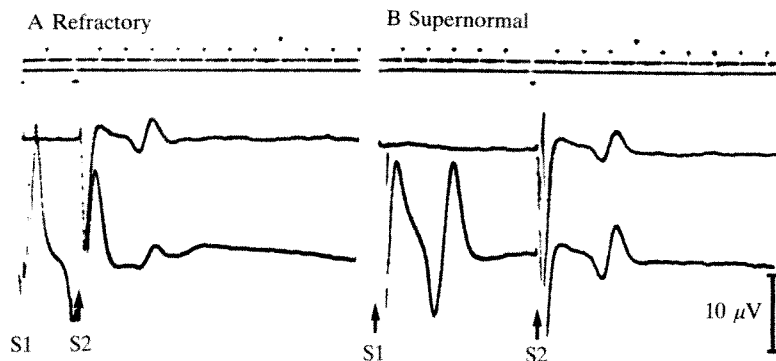


FIG. 1. Refractoriness (A) and supernormality (B) of low-threshold cutaneous afferents in the median nerve. The conditioning stimulus (S1) was supramaximal; the submaximal test stimulus (S2), of intensity 1.1 T, evoked a compound sensory action potential that was 20% of maximum. The responses to the unconditioned test stimulus are shown in the upper traces. The responses to the conditioning and test stimulus pair are shown in the lower traces for conditioning-test intervals of 2 ms (A) and 6 ms (B). The amplitude of the test volley was reduced by 30% in A and increased by 83% in B. Each trace is the average of 16 responses.

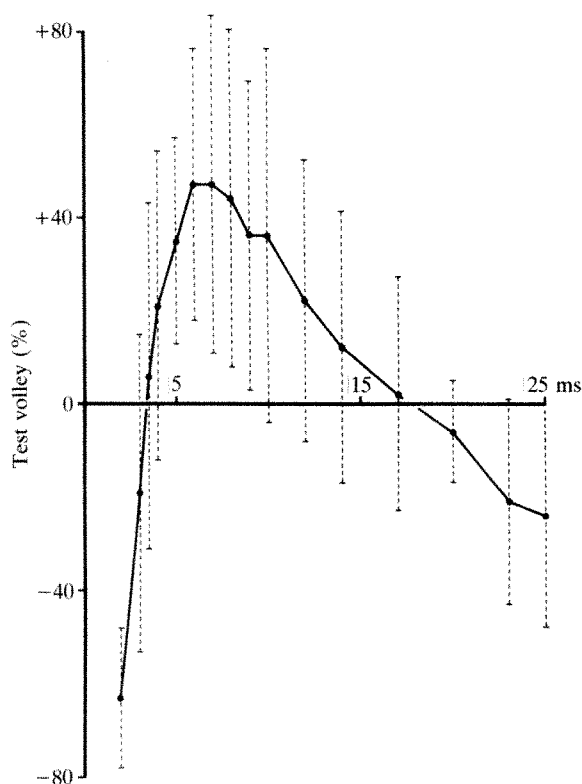


FIG. 2. The time course of the excitability changes in 20 normal subjects. The conditioning stimuli were supramaximal; the test stimuli (at 1.1–1.25 T) evoked cutaneous sensory volleys 20–40% of maximum. These afferents were relatively refractory to the test stimuli up to the 3.4 ms interval. The supernormal period lasts a further 14–15 ms before giving way to a second period of subnormality. Each data point is the mean  $\pm$  1SD.

the 2 ms interval averaged 7.3% ( $n=12$ ). At the 3 ms interval, the increase in latency was, on average, 3.8% for the same 12 subjects and 3.5% for all 20 subjects. The duration of the relative refractory period for these afferents was not determined precisely using increments in the conditioning-test interval of less than 1 ms. By interpolation on the graph of fig. 2, it lasted on average 3.4 ms.

### *Supernormal Period*

In all subjects, the relative refractory period was followed by a phase of supernormality in which the amplitude of the test volley was increased (figs 1B, 2). Changes in latency were small. At the interval producing greatest potentiation of amplitude, the latency decreased in 11 subjects, increased in 6 and did not change in 3. On average, the latency decreased by 2.8% but this was not statistically significant ( $P=0.77$ ). At first sight, this result seems at variance with Hopf *et al.* (1976) but the discrepancy could result from differences in technique. The present failure to demonstrate a consistent decrease in latency was not due to an inadequate sampling rate for the averager: at these intervals the binwidth was 0.02 ms, the sampling rate 50 kHz. However, Hopf and colleagues used a supramaximal test stimulus which would prevent an increase in amplitude from occurring but which would more accurately allow changes in latency to be detected (*see Discussion*).

Maximal potentiation of the test response occurred at conditioning-test intervals of 5 to 8 ms and was, on average, 47% (range 9–146%). The increase in excitability then decreased over approximately 10 ms, passing into a second phase of subnormality. This time course is similar to that described by other authors for human motor and sensory axons. In repeat studies on the same subjects, the time course and the extent of the excitability changes were reproducible (figs 3A, B), provided that (1) skin temperature was similar on the two occasions and (2) the test volleys were of comparable size, that is, a similar percentage of the maximal volley.

### *Effects of Temperature*

It is well established that cooling prolongs the relative refractory period. This was confirmed in pilot experiments for the present study, in which it was also found that the degree of potentiation in the supernormal period was small when skin temperature was below 30°C. In the subsequent study, extreme care was therefore taken to ensure that skin temperature did not fluctuate, remaining constant at close to 32°C. The averaged temperature recordings for the two sites for the 20 subjects were: mean 32.6°C, range 31–34°C. In the 2 subjects in whom the potentiation in the supernormal period exceeded 100%, skin temperature was 31°C, and the subject with smallest potentiation (9%) had a skin temperature of 34°C. For the 20 subjects, there was, paradoxically, a significant negative correlation between skin temperature and the degree of potentiation in the supernormal period ( $r = -0.6$ ,  $P < 0.01$ ). This was presumably due to the necessity to use radiant heat to warm the limb of some subjects, so producing a skin temperature higher than core or near nerve temperature.

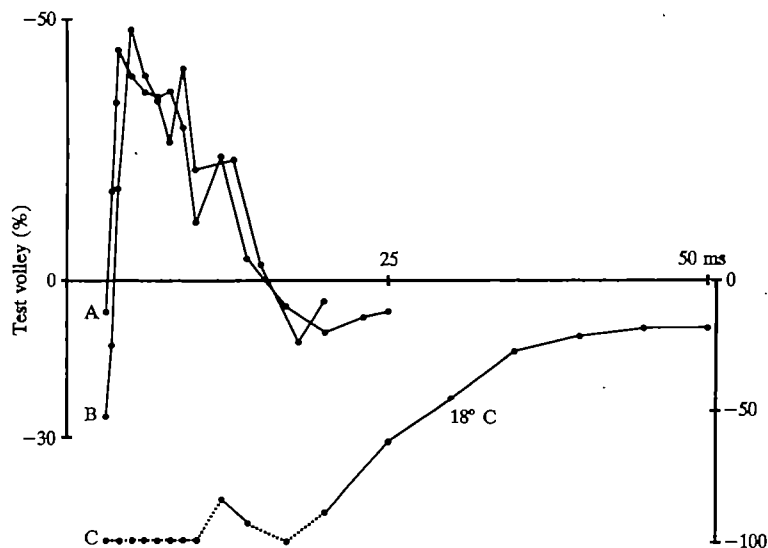


FIG. 3. Reproducibility of the excitability changes; the effect of cooling. Traces A and B are the excitability changes obtained under comparable conditions in two experimental sessions 30 days apart, with temperature maintained at or over 32°C on both occasions. Trace C was obtained in a third experimental session using comparable stimulating conditions, except for temperature, which was lowered to 18° by packing the limb in ice. The vertical scale on the left applies to A and B; the scale on the right applies to C.

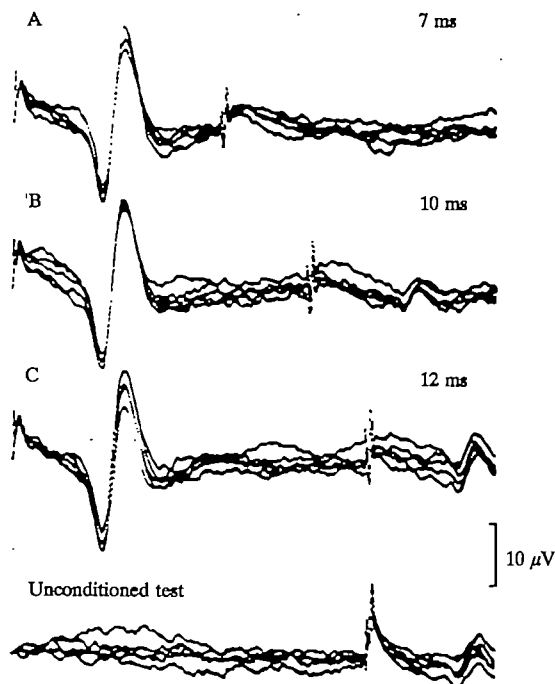


FIG. 4. The effect of temperature. Raw data (5 responses superimposed) obtained with a skin temperature of 28°C showing the effect of a supramaximal stimulus on a subsequent submaximal volley (test stimulus 1.2T) for conditioning-test intervals of 7 ms (A), 10 ms (B) and 12 ms (C). Trace D shows the unconditioned test volley. The test stimulus evoked no detectable afferent volley in A, a relatively small volley in B, and a volley slightly larger than the control amplitude in C.

In view of the above paradox, a systematic study of the effects of temperature was made in 2 experiments, lowering skin temperature by packing the limb in ice. This resulted in a marked prolongation of the relative refractory period, with a delay in onset of the supernormal phase and a decrease in the degree of potentiation during this phase. For the subject in figs 3 and 4, the maximal potentiation had been 44% and 48% at conditioning-test intervals of 4 ms and 5 ms, in two previous studies performed at skin temperatures of 32 and 33° C, respectively (fig. 3A, B). With a skin temperature of 28° C, the cutaneous afferents were still relatively refractory to the test stimulus at the 10 ms interval; the maximal potentiation in the supernormal period was only 10%, and occurred at the 12 ms interval (fig. 4). With further reduction in skin temperature to 18° C, the supernormal period was abolished so that the relative refractory period extended into the late subnormal period, still with incomplete recovery to the control level at a conditioning-test interval of 100 ms. The data to 50 ms are plotted in fig. 3C.

### *Size of the Test Volley*

The data presented in fig. 2 for the 20 subjects were obtained using test potentials 20 to 40% of maximum. Even within this limited range, there was a significant negative correlation between the degree of potentiation in the supernormal period and the size of the test volley (fig. 5;  $r = -0.45$ ,  $P < 0.05$ ). From these data it can

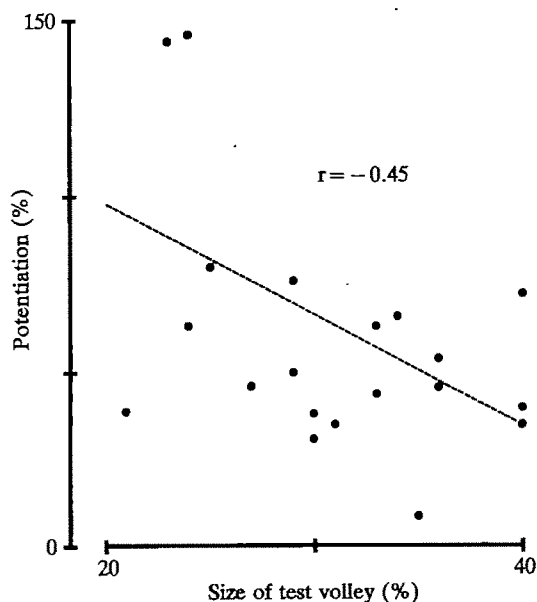


FIG. 5. The effect of the strength of the test stimulus. For the 20 subjects, the maximal potentiation of the test afferent volley in the supernormal period is plotted against the size of the unconditioned test volley (as a percentage of the maximal volley). There is a negative correlation which, using linear regression, is significant ( $r = -0.45$ ,  $P < 0.05$ ). The interrupted line represents the regression line.

be estimated that approximately 20% of the variability in the degree of potentiation seen in the group of subjects can be attributed to differences in the amplitude of the unconditioned test potential.

The effect of varying the size of the test volley as a percentage of the maximal volley was investigated in greater detail in 5 subjects. The time course of the excitability changes was not altered appreciably, but the degree of potentiation was significantly smaller the larger the test volley (fig. 6). For each of the 5 subjects,

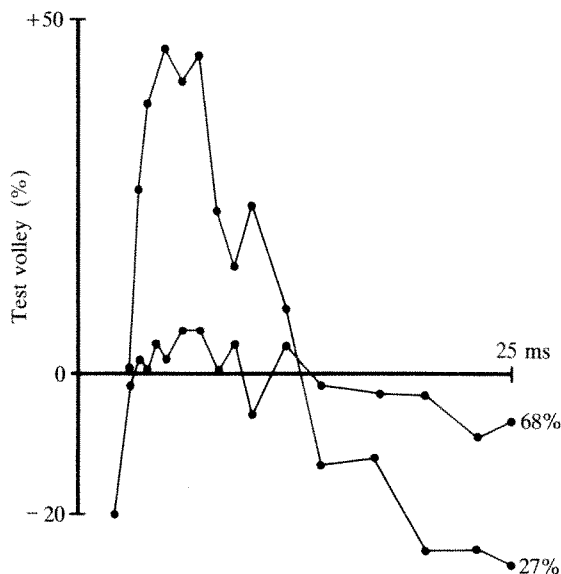


FIG. 6. The effect of the strength of the test stimulus. Excitability changes for the 1 subject using a weak test stimulus (unconditioned test volley 27% of maximum) and a strong test stimulus (unconditioned test volley 68% of maximum). Temperature was maintained over 32.5°C during both sequences.

the size of the test volley as a percentage of the maximal volley was varied, while keeping the conditioning-test interval constant. The chosen interval was that at which the degree of potentiation was maximal for the particular subject. The degree of potentiation varied inversely with the size of the unconditioned test volley in an approximately exponential manner (fig. 7). This result would be expected if, at each stimulus level, a similar number of additional fibres were to be recruited into the conditioned afferent volley, because the degree of potentiation was measured as a percentage of the unconditioned test volley. However, this may not be the entire explanation: when the potentiation was expressed in absolute terms ( $\mu\text{V}$ ), the degree of potentiation still decreased with increase in size of the test volley in each subject. When the test volley was 20 to 30% of maximum, the average potentiation was  $2.5\mu\text{V}$ , but when it was 60 to 80% of maximum, the average potentiation was  $0.6\mu\text{V}$ . This difference is significant ( $P < 0.05$ , *t* test for paired data).

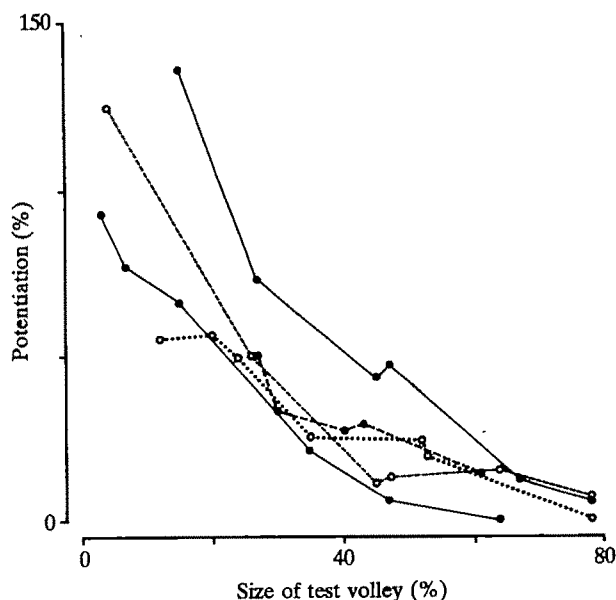


FIG. 7. The effect of the strength of the test stimulus. Data for 5 subjects. The strength of the test stimulus was altered so that the unconditioned test volley varied between 10 and 80% of maximum. For each subject, the experiment was performed at the conditioning-test interval that gave the maximal potentiation (between 5 ms and 8 ms).

### *Posttetanic Paraesthesiae*

In 12 experiments in 8 subjects, the digital nerves of the index or middle fingers were stimulated repetitively at 200 Hz for up to 10 min in order to induce paraesthesiae in the distribution of the stimulated nerves. The stimulus level was set to produce a near maximal compound sensory action potential ( $>80\%$ ; see fig. 8B). During the stimulus train, the subjects reported an intense but tolerable tingling sensation involving the whole digit, and also that the digit appeared to flex and/or rotate at interphalangeal joints. These illusions have been studied in greater detail by Gandevia (1985). During and following the stimulus train, the acuity of cutaneous tactile sensation was attenuated. Distinct paraesthesiae were not felt unless the duration of the stimulus train equalled or exceeded 5 min. They began some 20 to 30 s after the end of the stimulus train, increased in frequency over some 60 s, were associated with dysaesthesiae in response to skin stroking, and persisted for more than 10 min. The paraesthesiae appeared irregularly, referred to multiple discrete cutaneous sites, each of a size comparable to the receptive fields of cutaneous mechanoreceptors (see Hagbarth *et al.*, 1984).

Repetitive stimulation of an axon at high frequency produces a long-lasting depression of its excitability, both in animals (e.g., Gasser, 1935; Raymond, 1979; Bostock and Grafe, 1985) and in human efferent fibres (Bergmans, 1970). In human sensory axons, it proved difficult to demonstrate a comparable phenomenon using the stimulus parameters that result in posttetanic paraesthesiae (200 Hz for 10 min, at a level producing an afferent volley  $>80\%$  of maximum). During the tetanic



train, there was usually little decrease in size of the compound sensory action potential evoked by each stimulus but, if there was, stimulus intensity was increased slightly. In 5 experiments using a constant-voltage source as stimulator, the same stimulus level appeared to evoke a *larger* afferent volley when tested 30 s after cessation of the tetanic train (fig. 8). However, in 3 of these experiments the stimulus

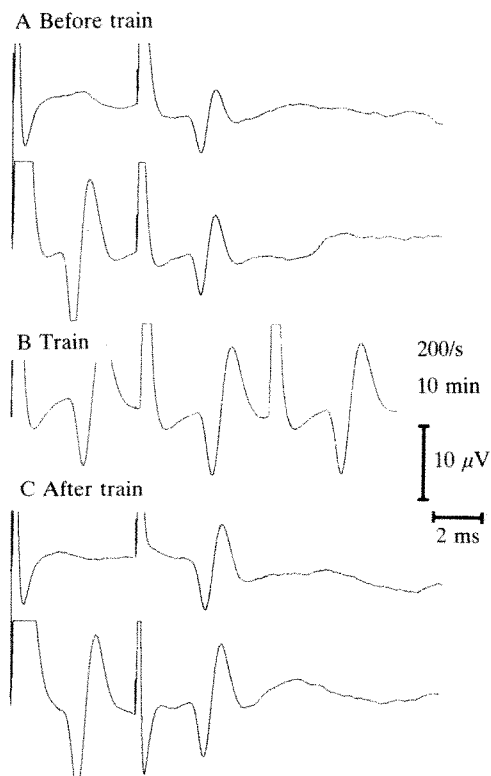


FIG. 8. The effects of prolonged high-frequency stimulation on axonal excitability. The digital nerves of the middle finger were stimulated at 200/s for 10 min using a stimulus intensity that produced a compound sensory action potential 82% of maximum (B). In A and C, the upper traces show the unconditioned test potential, and the lower traces the potentials evoked by the conditioning and test stimuli at the 5 ms interval. The stimuli were delivered from a current-voltage source at 9 mA (conditioning) and 4 mA (test). In A, the unconditioned and conditioned test potentials were 8.2  $\mu$ V and 10.1  $\mu$ V, respectively, the degree of potentiation being 23%. The response in C were recorded 30 s after cessation of the tetanic train, and the unconditioned and conditioned test potentials were 10.9  $\mu$ V and 14.3  $\mu$ V, respectively, the degree of potentiation being 32%. The conditioned test volley in C (14.3  $\mu$ V) reached 70% of the maximal compound afferent potential (20.4  $\mu$ V).

current was measurably greater, indicating that the repetitive stimulation had decreased skin resistance. Because the accuracy of the current monitor ( $\pm 1$  mA) was inadequate to ensure that the stimulus current did not change, the experiments were repeated using a constant-current source. In 5 experiments on 4 subjects, using a constant-current source, test potentials 34 to 36% of maximum were potentiated 30 s after the 10 min tetanic train to 112%, 120%, 122%, 138% and 138% of the pretetanus amplitudes. At this time, each subject reported multiple distinct paraesthesiae.

Posttetanic depression of axonal excitability was demonstrated in 2 subjects using stimulus trains of varying length (0.5, 1, 2, 3, 5 min, etc). Again, test stimuli were delivered from a constant-current source 30 s after the cessation of each train. The next longest train in the above sequence was then delivered, some 60 s after the end of the previous train. In 1 subject the test stimulus was set at 1.1 times threshold, evoking a compound sensory action potential 28% of maximum. After the 30 s tetanus the test potential was decreased to 8% of its original size. Following longer tetanic trains, the amplitude of the test potential gradually recovered towards the control size, reaching 88% following the 5 min tetanus. At this point the digital nerves had been subjected to a cumulative total of 11.5 min of stimulation. In the second subject, the test stimulus was set at approximately 1.25 times threshold, evoking a compound sensory action potential 50% of maximum. Initially, the depression of the test potential was progressive, greatest after the 3 min train (amplitude decreased to 62%), but by the end of the 5 min tetanus it had recovered to 73%. With both subjects, clear and distinct paraesthesiae were noted when the posttetanic depression was lessening: in subject 1, following the 5 min train (cumulative total of 11.5 min stimulation); in subject 2, after the 7 min tetanus (cumulative total of 16.5 min stimulation).

In all subjects, repetitive stimulation increased the magnitude of supernormality, whether tested at a fixed conditioning-test interval (5 subjects) or at multiple intervals (2 subjects). At fixed conditioning-test intervals of 5 ms in 4 experiments and 6 ms in a fifth, the degree of potentiation in the supernormal period was greater 30 s after the stimulus train than before it. In 3 of these experiments, the larger test volley was potentiated by a greater amount after the train than the smaller test volley had been before the train. This is illustrated in fig. 8, in which before the train (A), the test potential was 8.2  $\mu$ V (unconditioned) and 10.1  $\mu$ V (conditioned), the degree of potentiation being 23%. After the train (C), the test potential was 10.9  $\mu$ V (unconditioned) and 14.3  $\mu$ V (conditioned), the degree of potentiation being 32%. In view of the inverse relationship between the degree of potentiation and the size of the unconditioned test volley in figs 5–7, the greater potentiation of a larger test volley can be explained only by a change in the supernormal period induced by the stimulus train. In the remaining 2 of these 5 experiments, the potentiation of the larger test volley was less after the train than before it, and the intensity of the test stimulus was therefore reduced so that the posttrain test potential matched the pretrain test potential in size. When this was done, the degree of potentiation occurring in the supernormal period was greater following the train (22.9% and 35.7%) than before it (14.6% and 23.4%, respectively).

The measurements in the preceding paragraph were based on a single conditioning-test interval and may underestimate the maximal supernormality following a 10 min stimulus train, because prolonged high-frequency stimulation could distort the time course of the supernormal period, much as can occur following a period of nerve ischaemia (Stöhr, 1981b; Stöhr *et al.*, 1981). The time course of the supernormal period was monitored in 2 subjects before and after the

sequence of repeated tetanic stimulations (cumulative totals of 21.5 min stimulation for subject 1 and 28.5 min for subject 2). In both experiments, the maximal potentiation in the supernormal period was more than doubled, but occurred at conditioning-test intervals of 15 to 30 ms. In subject 1, the test potential was still increased by 9.5% at a conditioning-test interval of 40 ms, and in subject 2 by 28% at 50 ms. In subject 1, supernormality did not begin until the 6 ms interval following the stimulus trains, but had been maximal at 4 to 5 ms before the trains.

## DISCUSSION

In this study, the supernormal period of human cutaneous afferents has been documented, and evidence of increased excitability has been found in an experimental model of paraesthesiae. The technique described is simple and reproducible, and it allows a different aspect of peripheral nerve function to be examined using routine diagnostic equipment.

### *Comparison with Other Studies on Man*

The possibility that alterations in axonal excitability and in the ability to conduct an impulse train might be responsible for some of the symptoms occurring in peripheral nerve disease has prompted extensive studies in human subjects, including some of the supernormal period (single human motor axons: Bergmans, 1970; mixed cutaneous and muscle afferent fibres: Gilliatt and Willison, 1963; Stöhr, 1981a, b; Stöhr *et al.*, 1981; and cutaneous afferent fibres: Hopf *et al.*, 1976). Though different techniques have been adopted, the time course of the excitability changes are remarkably similar in these reports and the present. The current study standardizes a technique which, while it does not measure excitability directly, is simple and could be used easily as a diagnostic tool.

The technique of Bergmans (1970) depends on selective activation of the motor axon of lowest threshold innervating a select group of muscles. Bergmans has used it to elucidate many physiological phenomena in man, but its diagnostic applicability is probably more limited. Moreover, it cannot be assumed that the excitability changes that occur in motor axons following single or repetitive activation, following ischaemia or as a result of pathology are identical to those in sensory axons. For example, sensory axons are required to discharge transient and maintained impulse trains of much higher frequency than motor axons. The strength-duration curves of human afferent and efferent fibres differ (Paillard, 1955; Veale *et al.*, 1973). Removal of nerve compression produces paraesthesiae more readily than fasciculation, even when the compression has produced paresis of innervated muscles (unpublished observations).

Hopf *et al.* (1976) used supramaximal stimuli, both to condition and to test the excitability of cutaneous afferents. They sought, and demonstrated, a small decrease in conduction velocity (mean decrease 6%), but this change could be detected in

only 10 of their 12 subjects. They did not look for decreases in threshold excitability or for increases in amplitude of the test potential; indeed, their technique precluded any measurement of these changes. It would be difficult to use such a small and inconstant decrease in conduction velocity as the basis for a diagnostic test. Nevertheless, their technique demonstrated something which could not be confirmed in the present study or that of Stöhr (1981*a*), who measured threshold excitability. The explanation for both failures is probably related to proximal displacement of the effective point of stimulation with stronger stimuli: only with constant supramaximal stimuli will the lowest-threshold axons always be stimulated at precisely the same point.

Measurement of the stimulus strength required to produce a liminal afferent potential formed the basis of the studies of Gilliatt and Willison (1963), Stöhr (1981*a, b*) and Stöhr *et al.* (1981). The technique requires constant adjustment of stimulus intensity and, of necessity, the choice of a specific amplitude level to act as the limit of detectability. For example, Stöhr (1981*a*) quotes 'a clearly visible response of 0.1 maximal amplitude (2–4  $\mu$ V)'. It is debatable whether, in the diagnostic situation, changes in amplitude in response to a fixed submaximal stimulus provide a more reliable test than changes in stimulus strength necessary to produce a potential of fixed amplitude. Stöhr (1981*a*) used both techniques and reported that the 'magnitude of supernormality and subnormality is, however, more marked when using amplitude ratios, than with threshold ratios'. A limitation of the present technique is the wide range of amplitude potentiation seen in different subjects (9–146%), such that pathological increase or decrease in the degree of supernormality would not be detected unless the changes were absolute, that is, the test potential reached maximal amplitude or it could not be detected, respectively. Only Stöhr (1981*a*) has studied a sufficiently large group of subjects using threshold excitability to comment on intersubject variability: in 10 normal subjects, the maximal decrease in threshold ratio (i.e., hyperexcitability) was 12 to 20%. However, it is probable that pathological excitability will result in a change in the time course of the supernormal period, in addition to its magnitude. There are two experimental models of paraesthesiae due to ectopic impulse generation, ischaemia and repetitive stimulation, and in both the supernormal period is prolonged (Bergmans, 1970; Stöhr, 1981*b*; Stöhr *et al.*, 1981; present study). A change in the time course of the supernormal period would be detected whichever technique was chosen.

#### *Activity-Dependent Changes in Axonal Excitability*

There is an extensive literature on the time course of and the mechanisms involved in the oscillations in membrane excitability that follow an action potential in an axon. Qualitatively similar principles seem to hold whatever the species, mammalian or reptilian, and whatever the axon type, motor or sensory. However, there are quantitative differences between different types of axons and particularly between different species (*see* Discussion in Raymond, 1979), presumably dependent on the normal activity profile of those axons.

The supernormal and subnormal periods are associated with negative and positive afterpotentials, respectively (e.g., Gasser and Erlanger, 1930; Gasser, 1935; *see also* Raymond, 1979; Barrett and Barrett, 1982), and intracellular recordings confirm that the supernormality results from membrane depolarization. Although often attributed to an active potassium flux, the depolarization probably results from a passive electrical property of the myelinated axon, in both reptilian (Barrett and Barrett, 1982) and mammalian axons (Bostock and Grafe, 1985).

In reptilian and mammalian nerves, repetitive activation results in long-lasting hyperpolarization and a decrease in excitability. In general, the greater the activity the greater the depression of excitability (Gasser, 1935; Raymond, 1979; Bostock and Grafe, 1985). In single human motor axons, comparable excitability changes follow repetitive activation (Bergmans, 1970). This posttetanic depression of excitability can be attributed to an electrogenic sodium pump (Barrett and Barrett, 1982; Bostock and Grafe, 1985). At first sight, therefore, the finding in the present study of a larger test potential 30 s after prolonged high-frequency stimulation of human sensory axons is in conflict with a large body of established knowledge. However, mammalian sensory axons innervating, for example, the pacinian corpuscle and the spindle primary ending can transmit faithfully sensory information at 200 to 500 Hz. Much of the established literature has come from reptiles (Gasser, 1935; Raymond, 1979; Barrett and Barrett, 1982) or from motor axons in the ventral root (Bostock and Grafe, 1985) and peripheral nerve (Bergmans, 1970), and these axons do not maintain such high discharge rates, even transiently. In addition, the quoted studies have not subjected axons to the uninterrupted stimulation at such high frequencies for such a long period as in the present study, the sole exception being Bergmans (1970), who commented that the posttetanic depression of excitability of human motor axons was still demonstrable with stimulation as high as 300 Hz for 30 min.

This does not mean that human sensory axons do not undergo the same processes as are responsible for the posttetanic depression of excitability described by other authors. In two of the present experiments, depression could be detected when the stimulation protocol was altered. In reptilian nerves, tetanic stimulation produces two long-lasting opposite effects on axonal excitability, a long-lasting depolarization and a long-lasting hyperpolarization (Barrett and Barrett, 1982). The hyperpolarization normally dominates but the depolarizing afterpotential can be revealed when the hyperpolarization is eliminated by cooling (Barrett and Barrett, 1982). In rat ventral root fibres, the use of lithium to block the tetanic activation of the electrogenic sodium pump results in a complete block of the tetanus-induced hyperpolarization (Bostock and Grafe, 1985). 'Instead, a small *depolarization* and a *decrease* of the threshold were seen' (their italics). It is, therefore, not necessary to postulate any fundamentally different process to explain the present experimental findings.

*Posttetanic Paraesthesiae*

Prolonged repetitive stimulation of human sensory axons seems to produce two changes in excitability: axonal excitability may be elevated and the degree of supernormality following a single impulse is enhanced. Both changes would tend to allow generation of ectopic impulses in the hyperexcitable axons. Repetitive intrafascicular stimulation of a single axon results in abnormal discharges, both spontaneous and evoked, from that axon (Ochoa and Torebjörk, 1983). Post-ischaemic paraesthesiae are associated with abnormal neural discharges (Ochoa and Torebjörk, 1980) and, in the postischaemic state, the magnitude of the supernormality is enhanced (Bergmans, 1970; Stöhr, 1981*b*; Stöhr *et al.*, 1981). However, axonal threshold is elevated (Bergmans, 1970; Stöhr, 1981*b*), a change which would tend to oppose any tendency for ectopic impulses. Hence, although it is tempting to attribute posttetanic and postischaemic paraesthesiae to ectopic impulses set up in axons that have disturbed excitability, the apparently contrasting effects of these manoeuvres on axonal excitability remain to be resolved. Interestingly, in the two experiments in which repeated tetanic stimulation was performed without time for full recovery, paraesthesiae occurred when axonal excitability was still slightly below control values. These results and the postischaemic data of Stöhr (1981*b*) indicate that paraesthesiae can occur despite decreased axonal excitability, presumably dependent on the magnitude of the change in supernormality.

Of cutaneous mechanoreceptors, only the slowly adapting type II receptor maintains a spontaneous background discharge, and this discharge seems to evoke no definable tactile sensation (Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984). In the presence of an elevated threshold for impulse generation, as occurs following ischaemia, it is difficult to explain the apparently spontaneous occurrence of paraesthesiae, although it is perhaps less difficult to explain dysaesthesiae evoked by tactile stimulation. Perhaps only some of the disturbed afferents are active at any one time, their discharge triggered by an inapparent stimulus, such as the arterial pulse. However, this is probably also the case with posttetanic paraesthesiae which can be identified and localized to discrete punctate skin regions, even when profuse, and do not produce a continuous abnormal sensation involving the entire digital skin.

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# LABIAL KINEMATICS DURING SPEECH IN PATIENTS WITH PARKINSONIAN RIGIDITY

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## SUMMARY

Studies of orofacial motor control in Parkinson's disease (PD) have demonstrated that these subjects may exhibit hypokinesia and bradykinesia, as well as increased muscle tone. Yet the relationship between aberrations of orofacial movement and muscle rigidity remains unclear. Measures of labial muscle rigidity and movement were made for 12 parkinsonian and 9 age-matched control subjects. Displacement amplitude, peak instantaneous velocity, and movement time were evaluated during repetitive syllable productions. The results showed that while mean parkinsonian displacement amplitudes and velocities were lower than the normal control subjects, there was no statistical relationship between labial rigidity and the degree of movement abnormality. It is concluded that while rigidity may play a part in the overall disability, it does not sufficiently explain the labial articulatory difficulties associated with parkinsonism. This is in agreement with the literature on limb rigidity and movement aberrations in PD, suggesting that rigidity and bradykinesia may represent independent pathophysiological phenomena.

## INTRODUCTION

An increase in tonic background muscle activity and antagonistic cocontraction may coincide with rigidity and reduced movements in Parkinson's disease (PD). Ohye *et al.* (1965) contended that rigidity and reduced movements in PD were due to antagonistic cocontraction. Webster (1972) demonstrated a high correlation between the degree of rigidity and reduced velocity of arm movement in PD. Results on the benefits of pharmacological treatment in PD suggest that muscle rigidity and movement aberrations may stem from the same pathophysiology. Specifically, L-DOPA has been shown to be particularly useful in alleviating both akinesia and rigidity (Marsden and Parkes, 1977; Williams and Calne, 1981; Kobayashi, 1982). Several investigators have reported reduced muscular rigidity, increased movement velocity and/or decreased movement duration following the administration of L-DOPA (Draper and Johns, 1964; Bowen *et al.*, 1973; McLellan, 1973; Visser and Buist, 1973; Baroni *et al.*, 1984). Others have demonstrated that orofacial movements return to normal as background EMG is reduced following pharmacological intervention (Leanderson *et al.*, 1972; Nakano *et al.*, 1973).

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Nakano *et al.* investigated the relationship between tonic background EMG activity and qualitative features of articulatory movement. These investigators found that before treatment, reduced frequency and regularity of labial movement coincided with increased background EMG. A more quantitative and reliable investigation of the relationship between orofacial rigidity and movement was undertaken by Hunker *et al.* (1982) who found that PD patients who exhibited increased levels of labial stiffness also exhibited a reduced range of labial movements during speech.

On the other hand, there is also evidence to suggest that rigidity and akinesia may stem from separate mechanisms. For example, rigidity, akinesia and tremor may be independently modified by thalamotomy depending on the site of lesion (Hassler *et al.*, 1960; Selby, 1967). Hallet *et al.* (1977) failed to support the notion that slowness of movement was due to 'failure to relax' the antagonistic muscles. Instead, they found normal reciprocal EMG activity during ballistic arm movement in PD patients with bradykinesia. Evarts *et al.* (1981) measured reaction time (RT), movement speed and EMG correlates of muscular rigidity to determine the correlations between rigidity and movement aberrations in parkinsonism. Whereas movement time was generally more impaired than RT, there were patients who exhibited prolonged RTs in the absence of bradykinesia. These authors noted that an abnormal level of antagonistic EMG activity was not a factor in the prolongation of movement time. In fact, some rigid PD patients were able to make abrupt movements and many of the bradykinetic patients were not rigid. Thus it remains unclear whether an increase in background antagonistic muscle activity or rigidity is causally related to the movement disturbances in PD.

Further support for a separate mechanism hypothesis comes from research in the orofacial system in which serial measures of labial movements and labial stiffness were made over 3 h following the administration of Sinemet (M. P. Caligiuri and J. H. Abbs, unpublished observations). The results from 5 PD subjects demonstrated that labial stiffness and movement were not modified in parallel throughout the drug cycle, suggesting an independent action of L-DOPA on these two indices of orofacial motor control. On the basis of these findings, there may be separate pathophysiological mechanisms underlying orofacial rigidity and akinesia in PD.

Two hypotheses regarding the pathophysiology of hypokinesia and bradykinesia in PD may be posed on the basis of the above limb and orofacial studies: (1) that movement aberrations in PD stem from deficits in the regulation of muscle tone, namely, rigidity; and (2) that movement aberrations and disturbances of muscle tone are independent phenomena associated with parkinsonism. In the present study, muscle rigidity was quantified together with several kinematic parameters of orofacial movement. The aim of the investigation was to determine the extent to which increased levels of labial muscle stiffness coincide with abnormal labial movements during speech production.

## METHODS

*Subjects*

Twelve male parkinsonian subjects were selected for participation. All manifested at least mild limb rigidity and at the time of this investigation all were on a drug treatment regime consisting primarily of Sinemet. Subjects were evaluated to determine the presence and degree of axial and appendicular rigidity and disease severity. Disease severity was graded using the Hoehn and Yahr (1967) classification. Among the 12 PD subjects, 2 were in stage I, 7 in stage II, 2 in stage III and 1 in stage IV. Two subjects were taking benzhexol (Artane) and benztropine (Cogentin) in addition to Sinemet as part of their daily treatment regime. Drug therapies were not altered for the purpose of this study. PD subjects were evaluated for the presence of a motor speech disorder (dysarthria). Dysarthria was rated by three independent judges. Two PD subjects exhibited no dysarthria, 2 had mild, 5 had moderate, and 3 had severe dysarthria. Nine normal male subjects, matched for age and exhibiting no neurological or motor speech disturbances, served as controls (NC). Mean age for the PD subjects was 64.16 yrs and that for the control subjects 63.50 yrs.

*Measurement of Labial Rigidity*

**Apparatus.** The apparatus used to quantify the degree of labial muscle stiffness consisted of a linear motor (LM) instrumented with transducers to measure displacement and force. A lightweight aluminium paddle was attached to the shaft of the motor (*see* fig. 1A). Coupling of the shaft of the LM and the paddle was accomplished through a fine wire cable. The paddle rested gently on the lower lip at midline. The LM used in this study was controlled via an analog feedback circuit. The

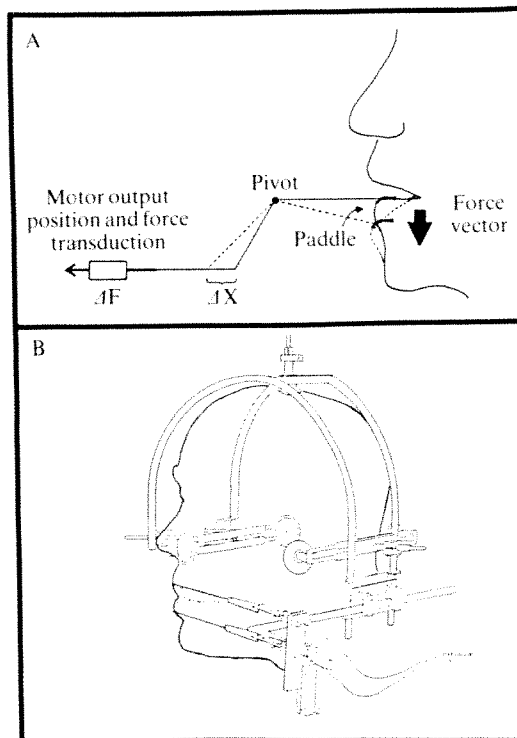


FIG. 1. Schematic drawings of the apparatus used to transduce labial stiffness (A) and labial movements during speech (B). Head-mounted movement transduction system after Barlow *et al.* (1983).  $\Delta F/\Delta X$  = coefficient of stiffness.

drive shaft was controlled so that its relative position was not influenced by any external change in force or displacement. In this manner, the LM operated in 'position feedback' as a means of autoregulating the imposed lip displacement. The LM was driven by computer-generated (PDP 11-44) ramp waveforms. These stimuli were characterized by rise and fall times of 50 ms and a plateau of 500 ms. The signal was low-pass filtered (using a digital 4-pole Butterworth filter with a 10 Hz cut-off), thus reducing the high acceleration associated with the onset of a ramp stimulus and eliminating the possibility of a reflex response to rapid stimulus onset. Stimuli consisted of waveforms having five different amplitudes ranging from 4 to 8 mm.

Two output signals were recorded from the LM. The first of these was a force signal representing the force necessary to displace the paddle inferiorly. This force output was transduced by a load cell attached near the tip of the motor's drive shaft. The load cell detected forces with a precision as low as 1 g. The second output signal was the position of the shaft. This was transduced by a linear voltage differential transformer (LVDT, Hewlett-Packard model 7-DCDT-050). The LVDT detected displacements to within  $\pm 0.20$  mm. Both the position and force signals were digitized at a sampling rate of 700 samples/s.

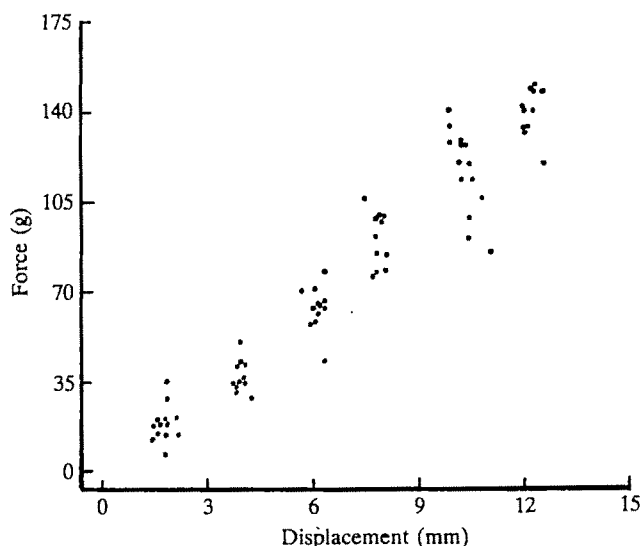


FIG. 2. Plot of the relationship between force and displacement. These data are from a single parkinsonian subject for passive displacement of lower lip.  $r=0.96$ .

**Procedures.** The degree of labial stiffness was determined by measuring the force necessary to displace the lower lip in an inferior direction. A similar technique was reported by Hunker *et al.* (1982) for quantification of labial stiffness and Tsementzis *et al.* (1980) for assessment of limb stiffness. Measurements of the peak force and displacement were made within the last 100 ms epoch of the 500 ms plateau of the displacement signal. The ratio of force to displacement was computed. Fig. 2 shows that force and displacement were linearly related throughout the range of displacements ( $r=0.96$ ).

Subjects were comfortably seated facing the LM and paddle apparatus. They were instructed to remain still and not to exert any resistance against the paddle. Shifts in labial force and position were monitored on-line in order to ascertain that the imposed lip displacements were initiated from the same baseline force and position levels for each trial. Stimuli were delivered only when the force output indicated baseline or 'rest'. Fifteen trials for each of 5 amplitudes were administered in random order to each subject. Thus the force/displacement ratio for 75 trials of passive labial movement

constituted the data set used to quantify the degree of labial rigidity. The mean coefficient for all trials was used as a dependent variable for subsequent group comparisons. Test-retest reliability of this measure was evaluated by comparing the coefficients obtained from the initial 75 trials with those obtained from an additional 25 trials elicited shortly afterwards. The results of paired-sample *t* tests indicated acceptable within-subject reliability.

#### *Measurement of Labial Kinematics for Speech*

**Apparatus.** Labial movements associated with speech production were recorded within 10 min following acquisition of the labial stiffness data. Movements were transduced using lightweight cantilever beams instrumented with strain gauges. Fig. 1B shows these cantilevers fitted to an aluminium head mount. Upper and lower lip movements were transduced in the inferior-superior (midsagittal) plane of motion. This system of transducing labial and mandibular movements during speech was initially reported by Abbs and Gilbert (1973) and subsequently by Barlow *et al.* (1983) as a valid technique for measuring labial and mandibular movements in patients with neurological disease.

**Procedures.** Once the head mounted cantilever beams were positioned appropriately, a bite-block was placed unilaterally between the upper and lower molars. The bite block (having an interincisor distance of 9 mm) was used to maximize labial movement and eliminate jaw movement. Subjects were instructed to repeat the syllable /va/ several times until told to stop. The syllable /va/ was selected to assess 'speech' kinematics because of the exclusive use of the lower lip in the production of /v/. Vocal intensity was monitored using an oscilloscope throughout the experiment. Subjects were instructed to maintain a constant level of vocal intensity throughout this phase of the experiment. Speaking rate has been shown to be an important variable influencing amplitude, duration and velocity of labial movement (Gay *et al.*, 1974; Tuller *et al.*, 1982; Caligiuri and Abbs, 1985). Speaking rate was controlled in the following manner. Subjects were instructed to repeat the monosyllable /va/ at least five times at four speaking rates: comfortable, slightly faster, faster, and as fast as possible. Not all subjects manifested the same speaking rates in response to the instructions. However, all subjects were able to repeat the syllable sequences within the 3 to 5 syllables/s range.

#### *Data Reduction*

Movement signals from five syllables per trial were computer indexed for quantitative analyses. Kinematic measures of labial elevation were made only on trials associated with speaking rates of 3 to 5 syllables/s. Fig. 3 shows an example of lower lip movement and the location of the analysis segments. The top trace represents displacement; the lower trace represents the instantaneous velocity. Analysis procedures initially involved digital filtering using a low pass four-pole Butterworth filter routine with a 30 Hz cut-off. The kinematic measures included (1) peak displacement amplitude, (2) peak instantaneous velocity, (3) movement time, and (4) time interval from movement onset to peak velocity. Analyses were made on as many as 25 syllable productions for each subject.

The principal hypotheses concerned whether the PD subjects exhibited increased labial muscle stiffness and reduced labial movements as compared with the control subjects. Thus one-tailed *t* tests were used to assess group differences on all labial motor control measures. In addition, correlation analyses were used to determine the presence of any relationship between labial stiffness and the four kinematic parameters.

## RESULTS

### *Labial Stiffness Results*

Fig. 4 displays stack plots of 10 trials for 1 rigid parkinsonian (PD) and 1 normal control (NC) subject. These 10 traces constituted the resultant labial force output

associated with 7 mm displacement input. For the PD subject, greater force (approximately 140 g) was required to displace the lower lip as compared with the NC subject (approximately 50 g).

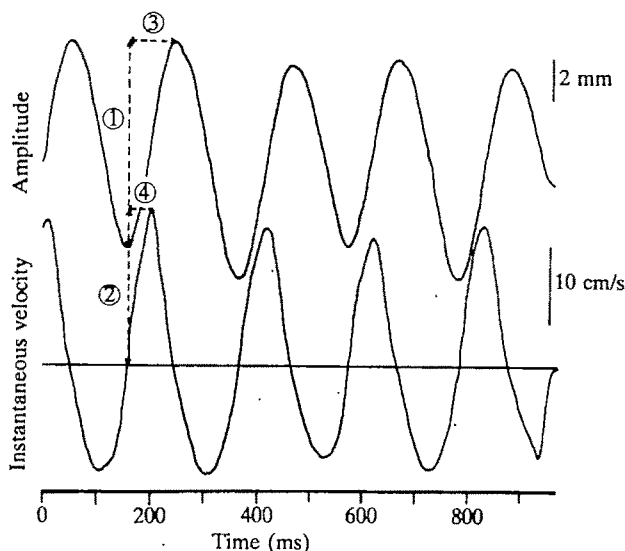


FIG. 3. Facsimile of lower lip displacement amplitude (*top*) and instantaneous velocity (*bottom*) for five repetitions of the syllable /va/. Circled numbers indicate location of the kinematic parameters: 1 = displacement amplitude; 2 = peak velocity; 3 = movement time; 4 = time interval from movement onset to peak velocity.

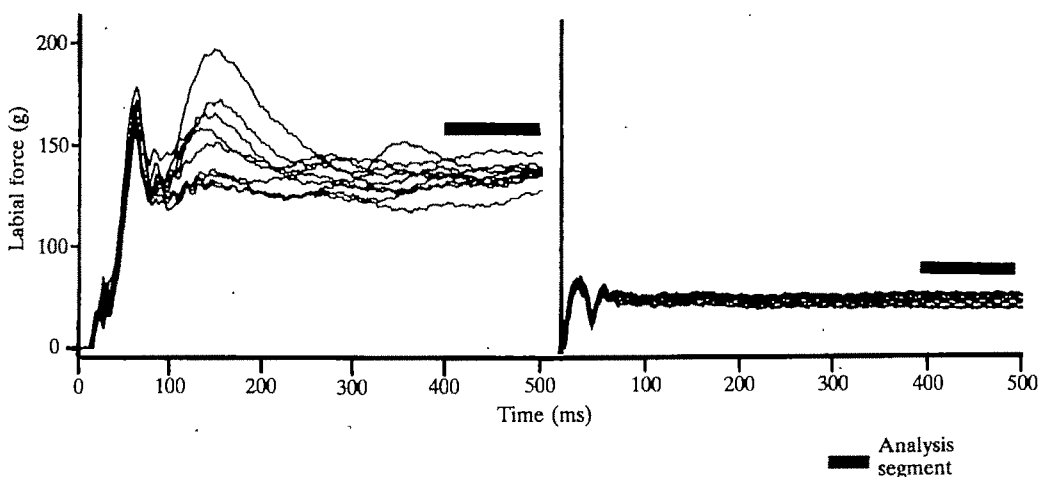


FIG. 4. Stack plots showing the resultant force associated with 10 trials of lip displacement (7 mm) for 1 parkinsonian (*left*) and 1 normal (*right*) subject. The segment analysed (100 ms) is indicated by the horizontal bar.

Table 1 shows the mean labial stiffness coefficients (individual subjects). The mean coefficient for the PD group was 10.49 (SD=5.59) while that for the NC group was 6.01 (SD=2.21). This difference was statistically significant ( $t=2.27$ ,

TABLE 1. INDIVIDUAL AND GROUP MEANS AND SDS FOR LABIAL STIFFNESS COEFFICIENTS FOR NORMAL CONTROL AND PARKINSONIAN SUBJECTS

| <i>Normal control subjects</i> | <i>Stiffness coefficient</i> | <i>Parkinsonian subjects</i> | <i>Stiffness coefficient</i> |
|--------------------------------|------------------------------|------------------------------|------------------------------|
| 1                              | 8.60                         | 1                            | 9.98                         |
| 2                              | 4.80                         | 2                            | 7.03                         |
| 3                              | 5.80                         | 3                            | 5.15                         |
| 4                              | 3.26                         | 4                            | 4.59                         |
| 5                              | 6.25                         | 5                            | 3.91                         |
| 6                              | 2.57                         | 6                            | 3.74                         |
| 7                              | 8.59                         | 7                            | 11.60                        |
| 8                              | 8.24                         | 8                            | 11.66                        |
| 9                              | 5.97                         | 9                            | 15.57                        |
|                                |                              | 10                           | 16.92                        |
|                                |                              | 11                           | 17.55                        |
|                                |                              | 12                           | 18.22                        |
| Mean                           | 6.01                         |                              | 10.49                        |
| SD                             | 2.21                         |                              | 5.59                         |

$P=0.017$ ). Previous studies have suggested that orofacial rigidity may be related to disease severity and/or dysarthria severity (Hunker *et al.*, 1982). Thus individual subject data were assessed using rank order correlation analyses to determine whether a relationship existed between labial stiffness and three descriptive measures of disease severity. A potential relationship was found between labial stiffness and dysarthria severity ( $r=0.67$ ,  $P<0.05$ ) and disease severity ( $r=0.59$ ,  $P<0.05$ ) but not for years postonset ( $r=0.31$ ,  $P>0.05$ ).

### *Labial Kinematic Results*

The results of the kinematic analyses for the PD and NC subjects are shown in Table 2. Control subjects had a mean labial displacement amplitude of 9.88 mm, while the PD subjects had a mean of 7.03 mm. This difference was statistically significant ( $t=2.72$ ,  $P=0.007$ ). Control subjects had a mean peak instantaneous

TABLE 2. DESCRIPTIVE STATISTICS INCLUDING MEAN AND SDS FOR FOUR KINEMATIC MEASURES FOR THE NORMAL CONTROL AND PARKINSONIAN SUBJECTS

|                      | <i>Amplitude (mm)</i> | <i>Velocity (cm/s)</i> | <i>Movement time (MT)* (ms)</i> | <i>Velocity. time (in % MT)</i> |
|----------------------|-----------------------|------------------------|---------------------------------|---------------------------------|
| Normal control (n=9) |                       |                        |                                 |                                 |
| Mean                 | 9.88                  | 14.93                  | 114.55                          | 0.47                            |
| SD                   | 1.83                  | 3.21                   | 18.55                           | 0.03                            |
| Parkinsonian (n=12)  |                       |                        |                                 |                                 |
| Mean                 | 7.03                  | 10.29                  | 114.83                          | 0.49                            |
| SD                   | 2.36                  | 3.86                   | 16.16                           | 0.08                            |

velocity for labial elevation of 14.93 cm/s, while the PD subjects had a mean of 10.29 cm/s. This difference was statistically significant ( $t = 2.92$ ,  $P = 0.004$ ). Movement times and time intervals from movement onset to peak velocity were not significantly different between the NC and PD groups.

### *Effects of Rigidity on Labial Kinematics*

The data in Table 1 suggest that the PD subjects comprised a heterogeneous group. They were separated into rigid and nonrigid subgroups on the basis of significant departure from the normal mean stiffness coefficient. Nonrigid PD subjects were those whose mean coefficients were within 2 SDs of the normal mean (i.e., less than 10.43); rigid PD subjects were those whose mean coefficients were greater than this value. The mean coefficient for the nonrigid PD group was 5.73, while that for the rigid PD group was 15.35.

Potential influences of parkinsonian subgroup differences on labial stiffness-kinematic relations are displayed graphically in fig. 5. This figure shows individual PD and NC subject data for displacement amplitude (top) and peak instantaneous velocity (bottom). The displacement amplitude and peak velocity data indicated that some rigid and nonrigid PD subjects exhibited normal labial movement. Nonsignificant correlations between labial stiffness and displacement amplitude ( $r = 0.01$ ) and labial stiffness and peak velocity ( $r = 0.12$ ) suggest that no relationship exists between orofacial rigidity and movement aberration for these PD subjects.

In summary, two groups of PD subjects may be identified: (1) rigid subjects who exhibit increased labial muscle forces to passive displacement, and (2) nonrigid subjects who exhibit normal labial muscle forces to passive displacement. The

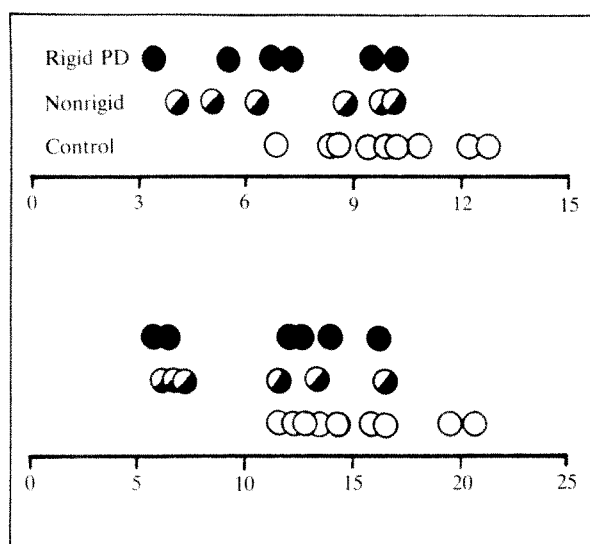


FIG. 5. Distribution of mean labial displacement (mm) (top) and peak instantaneous velocity (cm/s) (bottom) for three subject groups: normal control, rigid PD and nonrigid PD.



degree of this orofacial rigidity was unrelated to disease severity, but was related to the severity of the perceived motor speech disorder. Because most PD subjects were considered mild (9) and all subjects were being treated with Sinemet, the absence of labial rigidity in 6 PD subjects might reflect treatment rather than disease variation. The individual effectiveness of Sinemet in reducing appendicular and/or orofacial rigidity was not known. While many parkinsonian subjects exhibited reduced labial displacement amplitudes and peak velocities relative to normal controls, kinematic abnormalities were similar for both rigid and nonrigid PD subjects. That is, some rigid subjects produced the syllable sequences with normal labial amplitudes and velocities. At least 2 nonrigid subjects exhibited mean labial amplitudes and velocities well below the normal control mean.

### DISCUSSION

The observations on labial stiffness obtained in the present study are consistent with previous reports on orofacial muscle rigidity in parkinsonism (Denny-Brown, 1962; Hunker *et al.*, 1982). Using a similar measure, Hunker *et al.* reported increased labial stiffness for upper and lower lip muscles in 4 parkinsonian subjects. Leanderson *et al.* (1972), recording from lip muscles, reported that most of their parkinsonian subjects exhibited increased background electromyographic activity. It is apparent that muscular rigidity in PD is not limited to limb or axial muscles, nor is rigidity limited to muscles containing spindle receptors since labial muscles do not contain functional muscle spindles (Kadanoff, 1956; Lovell *et al.*, 1977).

Insofar as labial motor control is not regulated by a fusimotor system, labial rigidity cannot be attributed to an abnormal segmental mechanism. Similarly, limb rigidity appears not to be related to abnormal fusimotor drive (Burke *et al.*, 1977). Thus a central or suprasegmental mechanism may be responsible for limb as well as labial rigidity in PD. This notion is supported by findings implicating a deficit in the regulation of mechanoreceptive input to orofacial regions in experimental animals (Labuszewski and Lidsky, 1979; Welzl and Huston, 1981; Schneider *et al.*, 1982; Nishino *et al.*, 1985). Lesions to the substantia nigra pars reticulata in rats result in abnormal trigeminal responses including increased responsiveness to perioral touch (Nishino *et al.*, 1985). Schneider (1984), reporting on the influence of trigeminal stimulation on the basal ganglia, noted 'the most potent somatosensory influence on basal ganglia cells was cutaneous mechanosensory stimuli' (p. 1071). Thus orofacial muscle rigidity in PD may stem from a disturbance in the mechanism responsible for the indirect modulation of peripheral mechanoreceptive cutaneous input. Such a mechanism may involve afferent thalamic and cortical projections of the basal ganglia.

The bradykinesia and hypokinesia which characterize limb movements in parkinsonism may also be present in the orofacial system. This observation has been reported previously (Nakano *et al.*, 1973; Hirose *et al.*, 1981; Hunker *et al.*, 1982). In the present study, the PD subjects as a group exhibited labial hypokinesia and

bradykinesia. Some subjects, however, were able to produce labial movements for speech with normal amplitudes and velocities. It has been suggested that PD subjects produce speech with faster than normal rates (Netsell *et al.*, 1975). No physiological evidence for this phenomenon was found in the present study from analyses of peak velocities or movement times recorded from a single speech structure for simple unidirectional movements. It is possible that kinematic analyses of multiple segments of speech, including pause times, would reveal an abnormality of the sort described by Netsell and others.

The finding that labial rigidity was unrelated to any of the four movement parameters studied is inconsistent with previously reported data in parkinsonism. Hunker *et al.* (1982) found a qualitative relationship between levels of labial stiffness and reduced displacement amplitude among 4 subjects. However, they did not use formal statistical tests to evaluate the rigidity-hypokinesia relationship because of the small sample size. Evaluating this relationship with a larger sample of subjects apparently weakens the notion that rigidity underlies hypokinesia or bradykinesia in the orofacial system. Indeed, a weak relationship between limb rigidity and bradykinesia was reported by Martin (1967), Evarts *et al.* (1981) and Mortimer *et al.* (1982). Whereas it is generally agreed that rigid PD subjects have reduced movement amplitudes and velocities (Webster, 1972; Evarts *et al.*, 1981) the relationship between rigidity and movement is statistically weak. It may be hypothesized that orofacial rigidity and bradykinesia are independent phenomena. This notion has received support from other investigations of rigidity and akinesia in PD (see DeLong and Georgopoulos, 1981; DeLong, 1983). It is likely that, in PD, orofacial rigidity is centrally based and as such may be observed in parallel with bradykinesia in some patients. Furthermore, both motor phenomena may contribute independently to the disturbances in speech articulation associated with PD.

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## COMPARISON OF CORTICAL AND SUBCORTICAL LESIONS IN THE PRODUCTION OF POSTSTROKE MOOD DISORDERS

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### SUMMARY

Patients with single stroke lesions, verified by computerized tomography, involving either cortical tissue or restricted entirely to subcortical structures were examined for mood disorders. Those with left anterior lesions, either cortical or subcortical, had significantly greater frequency and severity of depression than patients with any other lesion location. A strong correlation between the severity of depression and proximity of the lesion to the frontal pole was observed for both left cortical and subcortical groups. Right hemisphere lesions did not show the same correlation with depression but were associated with a significantly higher incidence of undue cheerfulness.

These findings demonstrate the importance of the location of subcortical lesions in poststroke mood disorders and suggest that anterior subcortical structures may play an important but lateralized role in the production or regulation of mood.

### INTRODUCTION

For many years, clinicians have recognized that characteristic mood disturbances frequently follow focal brain injury. Kraepelin (1921) believed that focal brain lesions could sometimes be the direct cause of depressive disorders and Meyer (1904) noted that injury to specific brain regions was associated with particular psychopathology. Subsequent investigators found that lesions of the left hemisphere were commonly associated with depressed mood, sometimes termed depressive-catastrophic reaction (Goldstein, 1942; Gainotti, 1969), while right hemisphere damage was associated with an apathetic state accompanied by undue cheerfulness, sometimes termed indifference reaction (Babinski, 1922; Gainotti, 1969). Some investigators, however, have reported that after the acute poststroke period, depression may be found in equal frequency associated with either left or right

hemisphere lesions (Folstein *et al.*, 1977; Sinyor *et al.*, 1986). In addition to recognizing the importance of interhemispheric lesion location in the production of mood disorders following brain injury, several investigators have reported on the importance of the intrahemispheric lesion location to the type or severity of psychopathology (Benson, 1973; Robinson *et al.*, 1984a; Sinyor *et al.*, 1986).

In a study that included a selected group of patients with single lesions of the right or left hemisphere and no known psychiatric risk factors, we reported that left anterior lesions were associated with depression, particularly major depression, while right hemisphere anterior lesions were associated with inappropriate cheerfulness and apathy (Robinson *et al.*, 1984a). In addition to this general association of depression with left anterior lesions, the exact position of the left anterior lesion as identified by computerized tomography (CT) scan, was important. The distance of the anterior border of the lesion correlated significantly with severity of depression. We speculated that this strong association between lesion location and severity of depression might be explained by disruption of cortical noradrenergic pathways that arborize through the deep layers of cortex running from the frontal pole to posterior cortical regions.

Other investigators, studying patients with functional depression (i.e., depression with no demonstrable structural brain pathology), have recently noted metabolic abnormalities of subcortical structures in patients with unipolar depression (Baxter, 1985). In addition, basal ganglia dysfunction has been implicated in the pathogenesis of depression both in Parkinson's disease (Fibiger, 1984) and Huntington's chorea (McHugh and Folstein, 1975).

In our previous study of lesion location and mood disorders (Robinson *et al.*, 1984a), we did not differentiate cortical from subcortical lesions. Since subcortical abnormalities have been implicated in depressive disorders, we wanted to determine whether lesions that were purely subcortical by CT scan identification would be associated with the same type and severity of depressive disorders as cortical lesions and whether these findings would be compatible with our hypothesized role for biogenic amine neurons in the pathogenesis of poststroke depression.

In the present study, we report that subcortical structures play an important role in the induction of some poststroke mood disturbances and that the clinical-pathological correlations in patients with subcortical lesions are similar to those found in patients with mood disorders associated with predominantly cortical lesions.

## MATERIAL AND METHODS

### *Patients*

Patients included in this study were selected from two hospital populations: (1) 184 consecutive admissions to the University of Maryland Hospital for treatment of acute thromboembolic infarction or intracerebral haemorrhage; (2) a consecutive series of 68 patients admitted to the Montebello Rehabilitation Hospital for therapy following a cerebral infarct or haemorrhage. Detailed psychiatric examinations were performed on all patients, excluding only those who had severe comprehension

deficits or a markedly decreased level of consciousness. About 30% of these consecutively evaluated patients were excluded from further study.

For the present investigation, patients were included only if they were less than two months poststroke and if they had a single lesion demonstrable by CT scan which was blindly rated as being either cortical or subcortical. Patients with cortical lesions had predominantly cortical damage with only a small amount of subcortical involvement but never including the basal ganglia, thalamus and/or internal capsule. Patients with subcortical lesions had purely subcortical lesions with no involvement of cortical tissue.

Forty-five patients met the selection criteria: 16 patients had left cortical lesions, 9 had right cortical lesions, 13 had left subcortical lesions and 7 had right subcortical lesions.

#### *Neurological and Psychiatric Examination*

The neurological examination and diagnosis for all University of Maryland patients ( $n = 38$ ) was carried out using the criteria established by the Stroke Data Bank of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (Kunitz *et al.*, 1984). Patients at Montebello Hospital ( $n = 7$ ) received a standard clinical neurological examination. All neurological evaluations were performed blind to the findings on psychopathological examination.

After giving informed consent, patients were administered a series of standardized quantitative measures of mood, cognitive function, and physical impairment. We have previously shown (Robinson and Benson, 1981; Robinson and Szetela, 1981; Robinson *et al.*, 1983) that these instruments give reliable and valid measurement in this stroke population (note that patients with severe comprehension deficits were excluded from these studies). Examinations were administered in a private room between 11.00 am and 2 pm to minimize any possible effect of diurnal mood variation. The Hamilton Rating Scale for depression (Hamilton, 1960), a 17-item questionnaire measuring psychological and physiological symptoms of depression, was filled out by the interviewer. The Zung Self-Rating Depression Scale (Zung, 1965), a 20-item questionnaire, was read to each patient and their responses were scored on the four Zung categories. The modified Present State Examination (PSE) (Robinson *et al.*, 1983), a semistructured psychiatric interview that elicits symptoms related to depression and anxiety, was scored by the examiner. The Mini-mental State (Folstein *et al.*, 1975) and the Johns Hopkins Functioning Inventory (JHFI) (Robinson *et al.*, 1983) were also administered to each patient. The Mini-mental State is an 11-item examination that has been found to be reliable and valid in assessing a limited range of cognitive functions in stroke patients (Folstein *et al.*, 1975). Scores range from 0 to 30 and a score of 23 or below indicates cognitive impairment. The JHFI contains 10 items and evaluates degree of independence in activities of daily living such as walking, dressing, and eating. Scores range from 0 to 27, and higher scores indicate greater degrees of impairment (Robinson and Szetela, 1981).

Psychiatric diagnosis was established using DSM III symptom criteria for major depression or minor (dysthymic) depression (American Psychiatric Association, 1980). The symptoms used for these diagnostic criteria were elicited by the PSE. The method used to convert PSE symptoms to DSM III major or minor depression diagnosis is available upon request. The indifference reaction was also determined from symptoms elicited by the PSE. Patients who demonstrated any of the following symptoms without having a depressive syndrome were considered to have an indifference reaction: undue cheerfulness, euphoria, elation, subjective flight of ideas, high energy, subjective feeling of unusually good health, anosognosia, anosodiaphoria or pressure of speech.

#### *CT Scan Examination*

CT scans were read by one of us (S.E.S.) who was blind to the clinical findings. Although most of the CT scans were obtained from the University of Maryland Hospital (38/45) where the slice thickness and angle to canthomeatal line were consistent, the other scans also had a consistent slice thickness and angle of cut.

Lesion volume (expressed as percentage of total brain volume) was calculated from the ratio of the largest cross-sectional area of the lesion on any CT scan slice to the largest cross-sectional area of the whole brain on the slice passing through the largest cross-sectional area of the lateral ventricles. We have previously demonstrated the reliability of this procedure and its high correlation with other methods of determining lesion volume (Robinson *et al.*, 1985).

The anterior-posterior (A-P) location of each lesion was defined as the mean distance of the anterior border of the lesion from the frontal pole averaged over all slices in which the lesion was visible. This distance was expressed as a percentage of the maximum distance between the anterior and posterior poles on the CT slice where the lesion was identified. Similar procedures were applied in calculating A-P distances for both cortical and subcortical lesions. The posterior border of each lesion was calculated using the same methods. 'Anterior' lesions were those whose mean anterior border was less than 40% of the A-P distance and in the case of cortical lesions, showed at least partial involvement of frontal lobe tissue. 'Posterior' lesions were those whose mean anterior border was posterior to 40% of the A-P distance. All lesions were drawn on templates using the method of Matsui and Hirano (1978) to allow comparability between scan magnifications in the schematic display of lesions.

#### *Statistical Analysis*

Statistical analysis was performed using means and SDs, analysis of variance, Student's *t* test, and Pearson correlation coefficients. Frequency distributions were analysed using  $\chi^2$  tests with Yates' modification for expected cell sizes below 5.

## RESULTS

### *Patients*

Background information revealed no statistically significant differences between the four groups (Table 1). Patients were predominantly elderly black males in their 50s and 60s. All patients were right-handed, except for 2 left-handers and 1 ambidextrous patient. These 3 patients had left cortical lesions. Although 13 patients had a previous family and/or personal history of psychiatric disorders (10 with alcoholism), only 1 patient had a prior history of depression and there were no intergroup differences in frequency of depression or any prior psychiatric disorder. While patients were interviewed generally within the second or third week after the stroke, no interview was carried out after sixty days poststroke.

### *Neurological Findings*

There were no statistically significant differences in the frequency of motor or sensory impairments or handedness among the four groups. Most patients had a hemiparesis while less than half had sensory deficits or visual field defects (Table 2).

Seven of 29 patients with left hemisphere lesions and 2 of 16 patients with right hemisphere lesions, had intracerebral haemorrhages (Table 2). This distribution of infarcts and haemorrhages by location was not significantly different than a random distribution ( $\chi^2$ : ns).

Only patients with left hemisphere lesions had aphasia. Eight patients had cortical damage, while 1 patient had a subcortical lesion (Table 2).



TABLE 1. CHARACTERISTICS OF PATIENTS: LESION LOCATION

|                                                              | <i>L cortical</i> | <i>R cortical</i> | <i>L subcortical</i> | <i>R subcortical</i> |
|--------------------------------------------------------------|-------------------|-------------------|----------------------|----------------------|
| No. of patients                                              | 16                | 9                 | 13                   | 7                    |
| Mean age                                                     | 59 (12)           | 54 (13)           | 63 (12)              | 54 (8)               |
| Sex (% male)                                                 | 60                | 88                | 54                   | 57                   |
| Race (% black)                                               | 50                | 33                | 80                   | 100                  |
| Marital status (% married)                                   | 87                | 100               | 100                  | 86                   |
| Mean no. children                                            | 2                 | 2                 | 3                    | 3                    |
| Origin (% rural)                                             | 27                | 11                | 31                   | 14                   |
| Mean no. siblings                                            | 3                 | 3                 | 4                    | 3                    |
| Tobacco use (% > 1 pack/day)                                 | 44                | 22                | 23                   | 29                   |
| Previous medical illness (%<br>life threatening)             | 25                | 22                | 28                   | 29                   |
| Time since stroke (mean days)                                | 23 (25)           | 18 (14)           | 19 (21)              | 20 (19)              |
| Education (mean yrs)                                         | 9 (3)             | 11 (4)            | 9 (3)                | 8 (3)                |
| Family history of<br>psychiatric disorder (% of<br>patients) | 6                 | 23                | 11                   | 14                   |
| Personal history of<br>psychiatric disorder (%)              |                   |                   |                      |                      |
| Alcoholism                                                   | 19                | 15                | 11                   | 28                   |
| Other                                                        | 6                 | 0                 | 11                   | 14                   |

Figures in brackets indicate SDs.

### *Relationship of Lesion Location to Psychopathology*

Based on diagnosis, patients were classified in three groups: major depression, minor (dysthymic) depression and no depression. In the left cortical group, 4 of 16 patients had major depression, while 3 of 16 had minor depression. In the left subcortical group 4 of 13 patients had major depression, while 1 of 13 patients had minor depression. In the right cortical lesion group, 0 of 9 had major depression while 1 of 9 had minor depression. In the right subcortical lesion group 1 of 7 patients had major depression while none had minor depression. The hypothesis of unequal frequency of either major or minor depression based on left or right hemisphere lesion location was statistically substantiated ( $\chi^2 = 4$ ,  $df = 1$ ,  $P < 0.05$ ).

When intrahemispheric lesion location was considered, 3 of 5 patients with left anterior cortical lesions showed major depression, while the other 2 patients had minor depression. There were 2 of 11 patients with left posterior cortical lesions and depression: 1 had minor depression and the other had major depression. A hypothesis of unequal frequency of depression (major or minor) based on anterior versus posterior cortical lesion location was statistically substantiated ( $\chi^2$  Yates = 6.7,  $df = 1$ ,  $P < 0.01$ ).

Four of 6 patients with left subcortical anterior lesions had major depression while 1 patient with a left subcortical posterior lesion showed minor depression ( $\chi^2$ : n.s.).

TABLE 2. NEUROLOGICAL DEFICITS AND CT FINDINGS: LESION LOCATION

|                                           | <i>L cortical</i> | <i>R cortical</i> | <i>L subcortical</i> | <i>R subcortical</i> |
|-------------------------------------------|-------------------|-------------------|----------------------|----------------------|
| Paresis (mono or hemi)                    |                   |                   |                      |                      |
| Mild (%)                                  | 50                | 33                | 77                   | 100                  |
| Severe (%)                                | 6                 | 33                | 0                    | 0                    |
| Sensory deficit,<br>mono or hemi (%)      | 25                | 22                | 38                   | 0                    |
| Homonymous hemianopia (%)                 | 12                | 22                | 0                    | 14                   |
| Aphasia                                   |                   |                   |                      |                      |
| Broca (%)                                 | 12                | 0                 | 8                    | 0                    |
| Wernicke (%)                              | 31                | 0                 | 0                    | 0                    |
| Anomia (%)                                | 6                 | 0                 | 0                    | 0                    |
| Dysarthria (%)                            | 0                 | 15                | 0                    | 0                    |
| Handedness                                |                   |                   |                      |                      |
| (% right-handers)                         | 81                | 100               | 100                  | 100                  |
| CT findings                               |                   |                   |                      |                      |
| Infarct/haemorrhage<br>(% of patients)    | 80                | 88                | 62                   | 100                  |
| Lesion location<br>(% A-P distance)       | 32 (20)           | 39 (17)           | 36 (10)              | 36 (7)               |
| Lesion volume<br>(lesion area/brain area) | 9 (5)             | 11 (7)            | 3 (3)                | 4 (3)                |

Figures in brackets indicate SDs.

Combining cortical and subcortical groups, 9 of 11 patients with left anterior lesions showed depression, as compared with 2 of 9 patients with right anterior lesions. A hypothesis of unequal frequency of depression based on right or left anterior lesion location was statistically substantiated ( $\chi^2 = 7.1$ ,  $df = 1$ ,  $P < 0.01$ ).

Of 16 patients with right hemisphere lesions, 6 showed the indifference reaction. Three had cortical lesions (1 frontal and 2 posterior lesions), and 3 had subcortical lesions (2 anterior and 1 posterior). No patient with a left hemisphere lesion showed indifference. The hypothesis of unequal frequency of distribution of undue cheerfulness based on hemispheric lesion location was statistically substantiated ( $\chi^2$  Yates = 9.8,  $df = 1$ ,  $P < 0.01$ ).

Although mean PSE ( $F(3,41) = 0.74$ ), Zung ( $F(3,41) = 0.19$ ), and Hamilton ( $F(3,41) = 0.70$ ) scores of all patients with left hemisphere lesions were not significantly different from those patients with right hemisphere lesions, patients with left anterior lesions had significantly higher mean depression scores than patients with any other lesion location (PSE,  $F(3,41) = 7.29$ ,  $P < 0.003$ ; Hamilton,  $F(3,41) = 4.24$ ,  $P < 0.023$ ; Zung,  $F(3,41) = 8.20$ ,  $P < 0.003$ ). There were no differences in mean depression scores, however, between patients with left cortical and left subcortical lesions (Table 3) and between patients with right cortical and right subcortical lesions (Table 4).

In addition to finding higher depression scores among the patients with left

TABLE 3. LEFT HEMISPHERE LESION LOCATION AND DEPRESSION SCORES

|                            | <i>Anterior</i>                    |                                       | <i>Posterior</i>                    |                                       |
|----------------------------|------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------|
|                            | <i>Cortical</i><br>( <i>n</i> = 5) | <i>Subcortical</i><br>( <i>n</i> = 6) | <i>Cortical</i><br>( <i>n</i> = 11) | <i>Subcortical</i><br>( <i>n</i> = 7) |
| Depression scores (mean)   |                                    |                                       |                                     |                                       |
| PSE                        | 21 (8)*                            | 18 (10)*                              | 7 (10)                              | 4.5 (3)                               |
| Hamilton                   | 12 (7)**                           | 12 (5)**                              | 6 (5)                               | 4 (3)                                 |
| Zung                       | 53 (13)***                         | 54 (13)***                            | 34 (11)                             | 34 (8)                                |
| Cognitive impairment       |                                    |                                       |                                     |                                       |
| Mini-mental                | 18 (7)                             | 22 (5)                                | 18 (9)                              | 24 (2)                                |
| Activities of daily living |                                    |                                       |                                     |                                       |
| JHFI                       | 9 (9)                              | 8 (5)                                 | 6 (5)                               | 8 (3)                                 |

\* Compared with left posterior,  $P < 0.0004$ . \*\* Compared with left posterior,  $P < 0.003$ . \*\*\* Compared with left posterior,  $P < 0.0001$ . Figures in brackets indicate SDs.

TABLE 4. RIGHT HEMISPHERE LESION LOCATION AND DEPRESSION SCORES

|                            | <i>Anterior</i>                    |                                       | <i>Posterior</i>                   |                                       |
|----------------------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
|                            | <i>Cortical</i><br>( <i>n</i> = 4) | <i>Subcortical</i><br>( <i>n</i> = 5) | <i>Cortical</i><br>( <i>n</i> = 5) | <i>Subcortical</i><br>( <i>n</i> = 2) |
| Depression scores (mean)   |                                    |                                       |                                    |                                       |
| PSE                        | 16 (7)                             | 6 (3)                                 | 6 (5)                              | 7 (4)                                 |
| Hamilton                   | 10 (5)                             | 8 (4)                                 | 5 (3)                              | 7 (1)                                 |
| Zung                       | 42 (7)                             | 37 (8)                                | 43 (11)                            | 39 (1)                                |
| Cognitive impairment       |                                    |                                       |                                    |                                       |
| Mini-mental                | 20 (11)                            | 24 (12)                               | 23 (5)                             | 25 (6)                                |
| Activities of daily living |                                    |                                       |                                    |                                       |
| JHFI                       | 9 (8)                              | 3 (3)                                 | 7 (6)                              | 1 (1)                                 |

Figures in brackets indicate SDs.

anterior cortical/or subcortical lesions, the anterior-posterior location of the lesion was significantly related to severity of depression. Patients with left cortical lesions showed a significant inverse correlation between distance of the lesion from the frontal pole and both, PSE (fig. 1) and Zung scores (Table 5). In addition, patients with left subcortical lesions also showed an inverse correlation with both PSE (fig. 1) and Hamilton scores (Table 5).

Among patients with right hemisphere lesions, the only significant correlation was found in the cortical group where the distance of the lesion from the right frontal pole correlated significantly with the PSE score (Table 5). Depression scores were not significantly correlated with lesion location among the right subcortical lesion patients (Table 5).

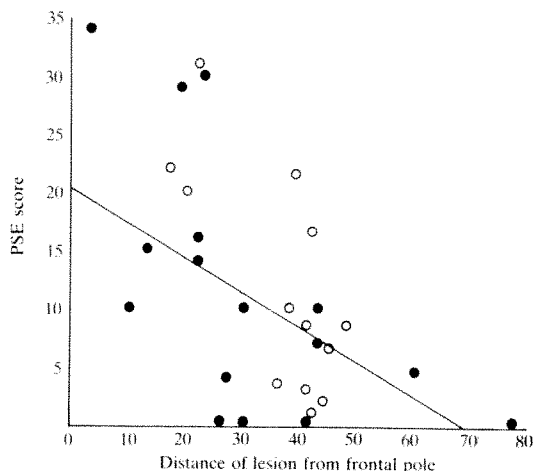


FIG. 1. Relationship between PSE score and distance of the anterior border of the lesion from the frontal pole for patients with either left hemisphere cortical lesions or left hemisphere subcortical lesions. The distance from the frontal pole is expressed as a percentage of the total anteroposterior distance. The regression line on the graph is based on the overall patient group. Filled circles=left cortical ( $r = -0.52$ ); open circles=left subcortical ( $r = -0.68$ ). Overall,  $r = -0.46$ .

TABLE 5. PEARSON'S CORRELATION COEFFICIENTS FOR DEPRESSION SCORES AND LESION LOCATION

|                          | PSE     | Hamilton | Zung   |
|--------------------------|---------|----------|--------|
| LC A-P distance (n = 16) | -0.52*  | -0.39    | -0.50* |
| RC A-P distance (n = 9)  | -0.65*  | -0.22    | -0.43  |
| LS A-P distance (n = 13) | -0.68** | -0.64*   | -0.33  |
| RS A-P distance (n = 7)  | -0.08   | -0.18    | -0.41  |

\*  $P < 0.05$ . \*\*  $P < 0.01$ . LC=left cortical lesions; RC=right cortical lesions; LS=left subcortical lesions; RS=right subcortical lesions.

Neither lesion volume nor mean posterior border of the lesion (determined the same way as anterior border) correlated significantly with depression scores in any of the four groups.

Templates showing the cross-sectional appearance of each lesion examined for this study are shown in fig. 2 for cortical lesions and fig. 3 for subcortical lesions.

#### *Relationship between Depression Scores and Physical and Cognitive Impairment*

Cognitive impairment, as measured by the Mini-mental State score, and activities of daily living, as assessed through the JHFI did not correlate significantly with any of the depression scales in any of the four groups. The Mini-Mental and JHFI scores were not significantly different between right or left cortical or subcortical groups (Mini-mental,  $F(3,41) = 1.61$ ; JHFI  $F(3,41) = 0.53$ ).

In spite of the fact that left anterior cortical and subcortical groups had sig-

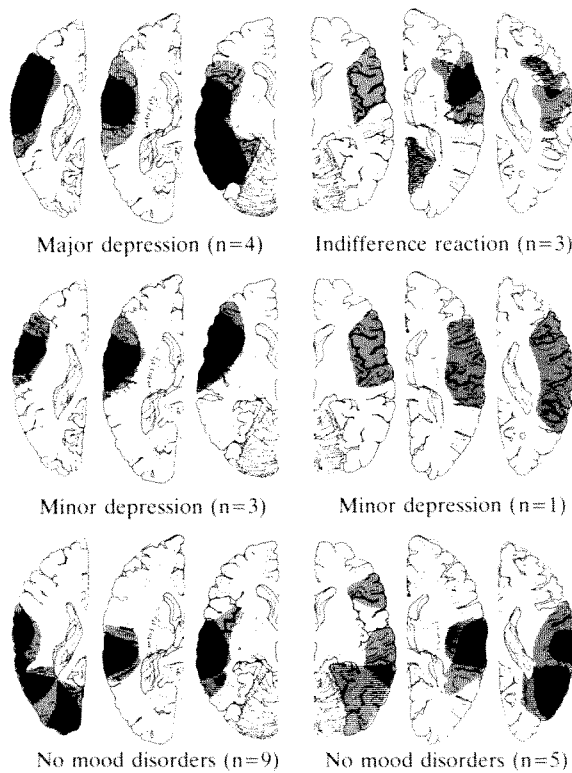


FIG. 2. Templates showing areas of lesion based on CT scan images for patients with left hemisphere cortical lesions (*left*) and right hemisphere cortical lesions (*right*).

nificantly higher depression scores than patients with left posterior cortical or subcortical lesions, these anterior lesion groups were not significantly more impaired than their respective posterior lesion groups in either Mini-mental State score ( $F(3,41)=0.41$ ) or activities of daily living (JHFI) score ( $F(3,41)=1.64$ ) (Table 3). Nine patients presented with aphasia. Eight had a left cortical lesion, while 1 had a left subcortical lesion. Three patients had a Broca aphasia (1 had major depression), 5 had Wernicke aphasia (3 had minor depression) and 1 patient had a nominal aphasia (without depression). Thus, among the 29 patients with left hemisphere lesions, 9 patients had aphasia and 4 were depressed, while 20 patients were not aphasic and 8 were depressed. The hypothesis of unequal frequency of distribution of depression based on the existence of aphasia was not substantiated ( $\chi^2$ : n.s.).

#### DISCUSSION

In the present study, we replicated our previous findings of more frequent and severe depression among patients with anterior left hemisphere lesions than with any other lesion location (Robinson *et al.*, 1984a). This time, however, we seg-

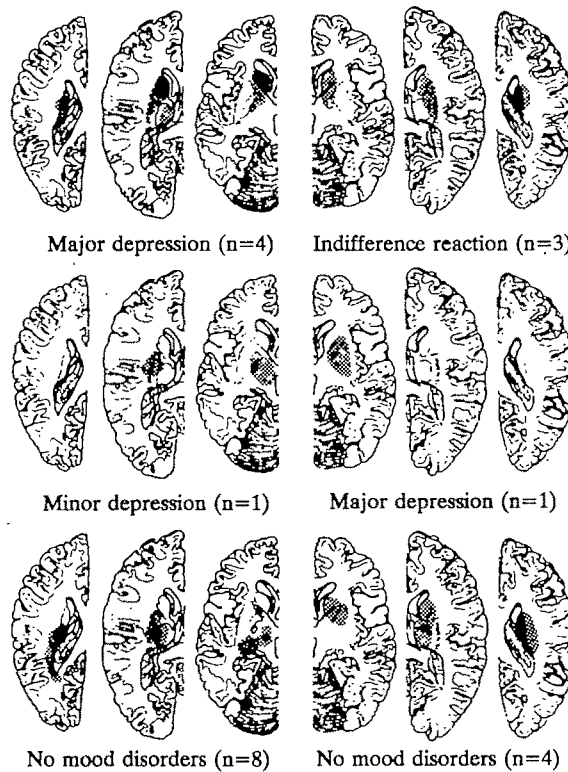


FIG. 3. Templates showing areas of lesion based on CT scan images for patients with left hemisphere subcortical lesions (*left*) and right hemisphere subcortical lesions (*right*).

regated our population based on CT scan evidence in two groups: those having cortical lesions without involvement of principal subcortical structures, and those having injury only in subcortical brain structures.

There were three significant findings from this study, although these findings were somewhat surprising to us. First, left hemisphere subcortical lesions were associated with the same frequency and severity of depression as cortical lesions; secondly, the correlation between distance of the lesion from the anterior pole and depression scores was at least as strong for left subcortical lesions as for left cortical lesions; and thirdly, left subcortical lesions have a different relationship to mood than right subcortical lesions. Although it might be expected that subcortical lesions may lead to depression because of their connection to other limbic structures, the anatomical specificity of the relationship to mood was surprising. That is, there was an important anterior-posterior correlation, with frontal-dorsal structures being most important.

These patients were evaluated during the first two months after stroke and we cannot be certain how these correlations might hold up over time. We have previously demonstrated, however, that poststroke depression lasts for more than six months, and that, during this time, depression continues to be significantly

correlated with left hemisphere lesion location (Robinson *et al.*, 1984b). On the other hand, we have also reported dynamic changes over the first six months poststroke in the relationship between lesion location and depression scores for patients with right hemisphere lesions (Robinson *et al.*, 1984b). Thus the longitudinal nature of these correlations may provide important insights into the neurophysiology of poststroke mood disorders.

The major methodological issues in this study are whether the population used (predominantly lower social class and black) and the exclusion criteria (severe comprehension defects with presumably posterior lesions) could have biased our results. Although we cannot be sure whether these findings have general application to other stroke patient populations, we think that the available data tend to refute the idea that our correlation of depression with anterior location is 'skewed' by exclusion of patients with comprehension deficits (i.e., posterior lesions). First, patients with mild comprehension deficits who were not excluded did not have a higher frequency of depression than nonaphasic patients (i.e., 3 of 5 Wernicke-type aphasics had minor depression and none had major depression, while 7 of 20 nonaphasic patients had major depression and 1 had minor depression). Secondly, patients with subcortical lesions who presumably had a lower frequency of comprehension deficits, had the same correlation with depression and lesion location as patients with cortical lesions. Finally, the 'clinical' impression about patients with comprehension deficits is that they are euphoric or occasionally paranoid (Benson, 1976).

Alexander (1980) reported depression in 4 of 15 patients with left hemisphere subcortical lesions. Watson and Heilman (1982) interpreted Alexander's findings as reflecting a low incidence of depression and suggested that a left subcortical lesion would fail to induce depression because it would not interrupt hemispheres processing of positive emotions, would not 'release' the depression-prone right hemisphere, and by disrupting the left corticoreticular system would affect the patient's arousability, thus leading to unawareness.

We previously reported in a study of patients with bilateral lesions that the induction of poststroke depression after a left hemisphere lesion does not seem to rely on a right hemisphere 'release' phenomenon, but depends on the anterior-posterior location of the left hemisphere lesion (Lipsey *et al.*, 1983). Alexander's (1980) finding of 27% of depression in his patients with left subcortical lesions is slightly lower than ours (38%). This may depend on lesion location in his patients, which was either thalamic ( $n=9$ ) or putaminal ( $n=6$ ). Our most depressed patients had lesions of the body and head of the caudate as well as in the anterior limb of the internal capsule.

The obvious question raised by the findings in the present study is how they might be explained. The first issue is why anterior subcortical lesions are associated with more severe depression than posterior lesions.

The results of this study suggest that anteriorly located subcortical structures such as the head of the caudate and/or the anterior limb of the internal capsule

may be involved in the production or maintenance of mood. One patient, who had a major depression (fig. 3), had a lesion restricted to the head of the left caudate, while 3 other patients who had lesions involving the head of the caudate on the left also had major depression. On the other hand, 2 of the 4 patients with involvement of the caudate on the right showed undue cheerfulness, while the other 2 did not show mood disorders (fig. 3). Recent evidence from other investigators is also consistent with the suggestion of caudate dysfunction in depression. Baxter *et al.* (1985) examined cerebral metabolic rates for glucose in patients with unipolar depression using F<sup>18</sup>-fluorodeoxyglucose positron emission tomography. They reported a significantly lower head of the caudate to whole hemisphere metabolic rate in this group as compared with normal controls. They also reported that the caudate to whole hemisphere metabolic ratio increased during recovery. Buschbaum *et al.* (1986) have also reported similar findings.

The question which next arises is how caudate dysfunction may lead to depression. Taylor *et al.* (1986) suggested that in Parkinson's disease, basal ganglia dysfunction may induce depression through disruption of frontal cortical function. Yeterian and Van Hoesen (1978) demonstrated that corticostriate projections originating from cortical regions which reciprocally relate via corticocortical connections, show at least one distribution area in the caudate. Thus the caudate is not only connected with main motor and sensory areas, but also shares common pathways with frontal cortical structures, which are reciprocally connected to numerous cortical areas. Perhaps these frontocortical-basal ganglia pathways are important in mood regulation and explain why we found the correlation between lesion location and severity of depression. Lesions which interrupt these frontal efferents closer to their origin may produce greater disruption of function and ultimately greater severity of depression. An alternative suggestion for the reason why anterior subcortical lesions produce depression is that the caudate might influence cortical function via one of its main efferents and principal pre-frontocortical afferent, namely the dorsomedian thalamic nucleus. Both cortical hypometabolism and diminished blood flow have been reported after restricted subcortical lesions (Metter *et al.*, 1983; Skyhøj Olsen *et al.*, 1986). These cortical dysfunctions might be more pronounced or more important to mood regulation following caudate lesions, thus leading to the correlation between lesion location and severity of depression. Thus whether subcortical lesions induce depression through cortical mechanisms or whether subcortical lesions produce depression through connection to other subcortical, perhaps limbic structures, is still uncertain.

A third possibility for explaining the importance of subcortical lesions in depression is the relationship of subcortical nuclei to ascending biogenic amine pathways. Disturbances of catecholaminergic systems have been frequently implicated in the aetiology of endogenous and Parkinson's disease depression (Fibiger, 1984; Holcomb *et al.*, 1983; Jaeckle and Nasrallah, 1985; Mayeux *et al.*, 1986). The catecholaminergic pathways arise in the brainstem and project anteriorly through the median forebrain bundle, disperse through the caudate and pass into the frontal



cortex. Lesions of the caudate may be more effective in disrupting these ascending pathways because of their dorsal position at that point, while more posterior lesions of the thalamus miss the majority of these ascending pathways because of their relatively ventral location in the posterior hypothalamus. This would also explain the correlation between lesion location and severity of depression since greater disruptions of these biogenic amine systems would occur with more anterior lesions.

The other interesting finding from this study is that right and left subcortical lesions have differential effects on mood. We have shown in a rat model of stroke that right and left cortical lesions have differential effects on catecholamine concentrations (Robinson, 1979). In addition, Oke *et al.* (1978) have shown that the biogenic amine distribution in the thalamus of humans is asymmetric. Recent work in our laboratory has also shown that right and left subcortical nucleus accumbens lesions have asymmetric effects on behaviour in the rat (Kubos *et al.*, 1987). Thus biochemical or structural asymmetries of subcortical as well as cortical structures may underlie this finding of differential frequency of depression depending on the hemispheric lesion location.

In conclusion, both left cortical and left subcortical lesions are associated with depression and both show an inverse correlation between the anterior distance of the lesion from the frontal pole and severity of depression. These findings suggest the importance of asymmetric subcortical mechanisms in mood regulation. Intra-hemispheric subcortical lesion location also relates differentially to mood with lesions of anterior structures having a greater effect on mood than posterior lesions. Further research using brain imaging techniques such as CT scan or magnetic resonance imaging may begin to define precisely which structures are most important in mood regulation and ultimately identify an anatomy and pathophysiology of depressive illness.

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# THE SLOW CHANNEL SYNDROME

## TWO NEW CASES

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## SUMMARY

Two patients are described with a myasthenic syndrome that presented in early adult life. One patient had 2 asymptomatic first degree relatives with similar electrophysiological findings. Both patients had abnormal fatigability, arm weakness being prominent; neither of them responded to anticholinesterase medication. An abnormal decrement at 3 Hz stimulation was present, and a single stimulus evoked a repetitive response. Electrophysiological studies on biopsied intercostal muscle showed miniature endplate potentials of normal amplitudes but with prolonged rise and decay times. Anticholinesterase staining (Case 1) was not reduced, and showed elongation of some endplates. Ultrastructural studies (Case 2) showed degeneration of junctional folds and diffusely thickened endplate basal lamina. Calcium deposits were not observed and myopathic changes were slight. The findings are consistent with a prolonged open time of the ACh-induced ion channel.

## INTRODUCTION

A small minority of the patients who are clinically suspected of myasthenia gravis (MG) have no serum antibodies against acetylcholine receptors (AChR) (Lindstrom *et al.*, 1976, Vincent and Newsom-Davis, 1980; Limburg *et al.*, 1983) and fail to respond convincingly to anticholinesterase drugs (Viets and Schwab, 1955; for review, see Oosterhuis, 1984). In such cases, disorders of the neuromuscular junction other than myasthenia gravis need to be considered. Among these is the congenital myasthenic syndrome attributed to a prolonged open time of the acetylcholine-induced ion channel, the so-called 'slow channel' syndrome, which has been described in 6 cases (Engel *et al.*, 1982). We describe in this paper 2 new

patients (one of whom had two subclinically affected first degree relatives) and we report new electrophysiological and morphological findings.

## MATERIALS AND METHODS

### *Clinical Data*

#### *Case 1*

This 28-yr-old married woman developed weakness of the upper arm in the eighth month of her first pregnancy when she was 23. Three weeks after delivery by caesarian section, weakness of her arms increased, particularly at the end of the day and she had transient difficulty in chewing. In the following year she noticed leg weakness after exercise, and she fell several times. On two occasions in one week, her right eye remained closed for 30–60 min after waking. She also experienced double vision while watching television.

MG was suspected when she was 25 yrs old. However, weakness was not reversed by injections of edrophonium or neostigmine, nor by oral pyridostigmine and ambenonium chloride. In fact she responded with sweating, nausea and fasciculations in the muscles of the face, appearing hypersensitive even to small amounts of anticholinesterase drugs. The EMG of the hand muscles showed a typical decrement of 25% at 3 Hz stimulation and no signs of a Lambert-Eaton syndrome. No antibodies to acetylcholine receptor (AChR) or to striated muscle were found. Since no other cause for her fluctuating weakness could be detected, the diagnosis of MG was thought probable and she underwent thymectomy. The thymus was histologically normal.

In the year after the operation her signs increased gradually (fig. 1), again without improvement by anticholinesterases. She was treated with prednisone, up to 80 mg (1.5 mg/kg body weight) on alternate days without any improvement. At that time it was suspected that she might have a myasthenic syndrome other than MG, and she was referred to J.N.D. (London). It was noted that she had mild wasting of all muscles of the hands and generalized weakness, although not all muscle groups were equally affected (Table 1). Tendon reflexes were all present. The combination of mild hand muscle wasting, myasthenic weakness, the absence of antibodies to AChR and edrophonium

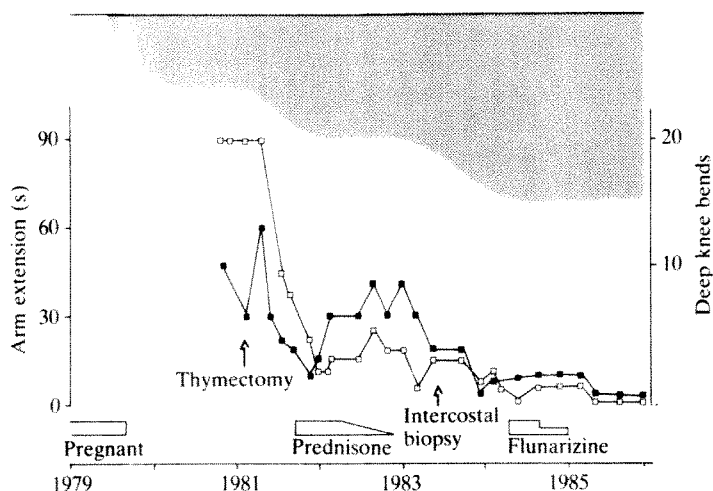


FIG. 1. Course of illness in Case 1. Shaded area: global intensity of the weakness. Open squares = number of deep knee bends; closed squares = arm extension forward (s). Initial prednisone dose 80 mg alternate days. Initial flunarizine dose, 20 mg/day.

unresponsiveness suggested the 'slow channel' syndrome. Electromyography was consistent with this diagnosis, showing a repetitive muscle response to single shocks (*see below*).

Her condition has continued to deteriorate but no ocular or bulbar symptoms have appeared. Flunarizine (Sibelium, a calcium influx blocker) 10 to 20 mg daily was without benefit. Her present status is given in Table 1. Muscle strength and endurance fluctuate, and are worst at night.

*Family.* Her father (aged 56 yrs), her mother (aged 49 yrs) and her brother (aged 34 yrs) had no symptoms or signs of weakness or fatiguability and showed no EMG abnormalities. Her parents were unrelated. Her 6-yr-old daughter had no weakness and had no repetitive muscle response to single shocks.

### Case 2

This 24-yr-old married woman, employed as a nurse, first developed intermittent weakness of the finger extensors at the age of 21, and her family noticed slight eyelid drooping. Serial photographs showed the insidious development of her ptosis from the age of 16 yrs and a change in her facial expression. She could not raise herself by her arms at gymnastics and at times she was unable to lift her arms repetitively; she had to give up her nursing work. At the age of 23 she also developed weakness of the legs. She was referred with the suspected diagnosis of MG, which seemed confirmed by the response to 3 Hz stimulation of the hand muscles. On examination she had a ptosis of about 25%, which slightly increased on lateral gaze. She lacked facial expression. She had well developed muscles and a rather athletic posture. After a period of rest the initial strength was normal in most muscles but she failed at endurance tests (Table 1). Walking on heels or toes was possible for only

TABLE 1. MUSCLE STRENGTH AND ENDURANCE TESTS

| Muscle strength*       | Case 1 | Case 2 |               |
|------------------------|--------|--------|---------------|
| Neck flexors           | 60     | 125    |               |
| Neck extensors         | 85     | 125    |               |
| Deltoid                | 15     | 80     |               |
| Biceps brachii         | 40     | 100    |               |
| Triceps brachii        | 55     | 115    |               |
| Three-point grip       | 45     | 100    |               |
| Hip flexors            | 30     | 75     |               |
| Gluteals               | 65     | 80     |               |
| Knee extensors         | 90     | 100    |               |
| Foot extensors         | 20     | 100    |               |
| Foot flexors           | 80     | 100    |               |
| <i>Endurance tests</i> |        |        | <i>Normal</i> |
| Extended arm test (s)  | 5-15   | 15-20  | > 180         |
| Extended leg test (s)  | 15     | 90     | > 60          |
| Deep knee bends (no.)  | 0-1    | 1-3    | > 30          |
| Head raising (s)       | 20-45  | 60     | > 60          |

\* Measurement of muscle strength with a hand-held dynamometer. Values are the % of the minimal values obtained in women of the same age and posture (Ploeg *et al.*, 1984).

three steps and her gait was waddling. Neurological examination was otherwise normal, tendon reflexes being easily obtainable.

A slight improvement of leg weakness was measured after administration of 1.5 mg neostigmine i.m. but the arm-raising time and the ptosis did not improve. Oral pyridostigmine seemed to increase her weakness and ephedrine had no effect. Antibodies to AChR were absent.

The clinical picture, the absence of anti-AChR antibodies, the poor response to anticholinesterases

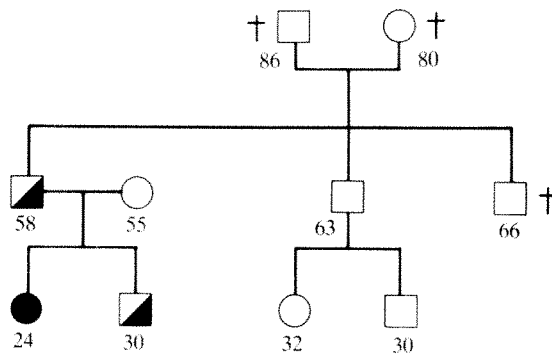


FIG. 2. Pedigree of Case 2. All living persons were examined clinically and electromyographically. ● = Case 2; ■ = subclinically affected; † = died, not examined, no history of weakness.

and the decrement at 3 Hz nerve stimulation, all similar to our first patient, suggest a myasthenic syndrome of the slow channel type. This was again supported by the typical finding of a repetitive muscle response to a single nerve stimulus.

*Family.* Her mother (aged 55 yrs), her father (aged 58 yrs) and her brother (aged 30 yrs) had no complaints of muscle weakness or undue fatiguability and showed normal strength and endurance at examination (fig. 2). However, the EMG in her father and brother showed the same repetitive response at stimulation at 0.2 Hz. Her father also had a decrement of the muscle response at 3 Hz stimulation. Her brother showed a decrement of 20% only after ischaemia. An intercostal biopsy of the father was investigated (*see below*). The father's brother and his son and daughter were clinically and electromyographically normal. Her paternal grandparents and another uncle had died; they had not had signs of muscle weakness (fig. 2).

## LABORATORY INVESTIGATIONS

In both patients normal values were found in routine biochemical tests, serum creatine kinase, thyroid function, immunoglobulins and creatine and creatinine in 24-h urine samples. Antibodies to AChR (repeated tests), to skeletal muscle and to antinuclear substance were absent. X-rays of the thorax and a computerized tomography of the mediastinum (Case 2) were normal. Computerized tomograms of the muscular system at six different levels showed normal muscle contours and densities.

### *Electromyography*

Repetitive stimulation studies were performed with surface-stimulating electrodes, and Ag/AgCl disc recording electrodes placed on the muscle belly and tendon insertion. Trains of 8 to 10 stimuli were delivered at 0.2, 1, 3 Hz and also at 3 Hz after 15 s maximum voluntary contraction; in addition, responses to single stimuli were recorded. The ulnar and median nerves were stimulated at the wrist with recording electrodes over the abductor digiti minimi (ADM) and abductor pollicis brevis (APB) muscles, respectively. The midclavicular point was stimulated with surface electrodes on biceps brachii and deltoid and the peroneal nerve was stimulated with electrodes on extensor digitorum brevis (EDB). Upper and lower limb motor and sensory conduction studies and concentric needle electromyography were performed according to standard techniques and single fibre EMG was performed on the extensor digitorum communis (EDC) using a Medelec SF25 needle electrode.

### Electrophysiology

*Case 1.* Intercostal muscle biopsy was taken under local anaesthesia (London). Microelectrodes were used to make intracellular recordings (23–25°C) as previously described (Wray, 1981). Miniature endplate potentials (mepps) were recorded in small muscle bundles in well oxygenated Krebs solution. At each endplate, 5–31 mepps were recorded. Acetylcholine (ACh, 1.1–1.4  $\mu\text{M}$ ) was applied in the bath in the presence of physostigmine (3  $\mu\text{M}$ ) and the membrane potential was recorded continuously. The voltage noise produced in this way was analysed as previously described (Wray, 1981). All recordings were stored on magnetic tape and analysed subsequently by computer. For mepps, the rise time was taken as the time required for the mepp to grow from 20 to 80% of peak amplitude. The mepp decay time ( $\tau$ ) was obtained by least squares fit of the decay phase, approximated as  $\exp(-t/\tau)$  over the range 80–20% of peak amplitude, where  $t$  is time. Control muscle was obtained from patients undergoing chest surgery.

*Case 2.* Intercostal muscle biopsies of both the patient and her father were taken under general anaesthesia (Utrecht). Mepps were recorded as in Case 1 at about 20°C except that a Ringer's solution was used instead of a Krebs' solution. The decay times of the mepps were assessed by manual computation.

Test and control values were compared using two-tailed Student's  $t$  test. All values quoted are means  $\pm$  SE, unless otherwise stated.

### <sup>125</sup>I- $\alpha$ -Bungarotoxin binding ( $\alpha$ -BuTx) and Acetylcholinesterase (AChE) staining

This was undertaken using the methods previously described (Vincent *et al.*, 1981).

### Morphology

Material from the muscle biopsy taken from Case 2, and from a control patient undergoing surgery for congenital heart disease, was used for light and electron microscopy. It was divided into three parts. One part was frozen in isopentane which was cooled in liquid nitrogen, and sections were stained for routine histology and histochemistry of muscle fibres, and according to the Pestronk and

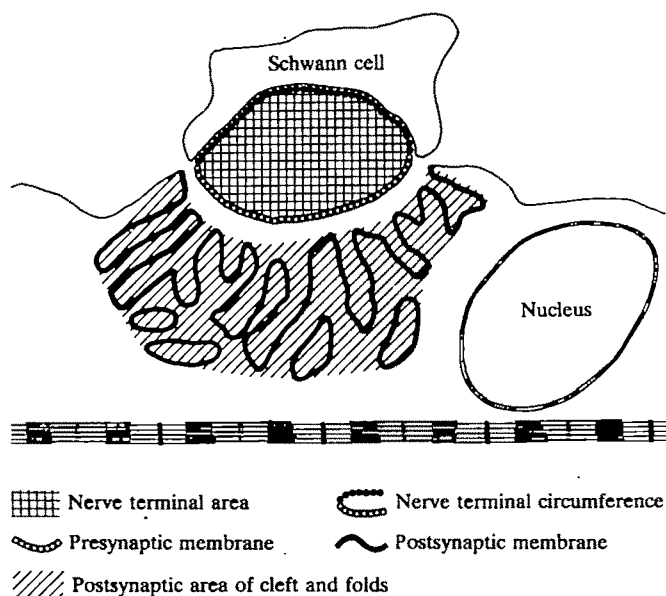


FIG. 3. Schematic representation of analysed parameters.



Drachman (1978) method for intramuscular nerves and endplates. A second part was immersed in oxygenated Tyrode solution containing  $5 \times 10^{-8}$  M a-BuTx. AChRs were made visible from sections in this part with an immunoperoxidase method (Daniels and Vogel, 1975). A third part was pinned out and fixed for 2 h in a 2% glutaraldehyde solution buffered with 0.1 N cacodylate buffer (pH 7.3) containing 10 mM  $\text{CaCl}_2$ , postfixed in 1% osmium tetroxide solution, dehydrated and embedded in epon as in routine procedures for electron microscopy.

Motor endplates were identified in  $1 \mu\text{m}$  sections stained with toluidine blue. Ultrathin sections from endplate-containing regions were contrasted with uranyl acetate followed by lead citrate and viewed in a Zeiss 109 electron microscope. A neuromuscular junction was defined as a nerve terminal with synaptic vesicles and a postsynaptic area of folds and clefts associated with it. An IBM-PC (Boca Raton, Florida, USA) with graphic tablet (Calcomp, Scottsdale, Arizona, USA) was used for quantification. The analysis included the nerve terminal area, the presynaptic membrane length and the postsynaptic membrane length. The postsynaptic area and the postsynaptic membrane density as defined by Engel and Santa (1971) were also measured (fig. 3). In addition, we determined the ratio of presynaptic membrane length to nerve terminal circumference as a measure of the extent to which the nerve terminal was surrounded by Schwann cell. Statistical analysis of the quantitative data was made by means of the nonparametric Mann-Whitney U test.

Von Kossa silver and Alizarin red methods for the demonstration of calcium deposits were performed as described by Pearse (1985).

## RESULTS

### *Case 1*

#### *Electromyography*

A decrement in the compound muscle action potential (CMAP) at 3 Hz nerve stimulation was obtained in ADM, APB, deltoid and EDB muscles. Decrements ranged from 15 to 40% and were reduced considerably after 15 s maximum voluntary contraction; there was a small increase in the initial CMAP after exercise. There was a repetitive response to single stimuli in all muscles tested (fig. 4A),

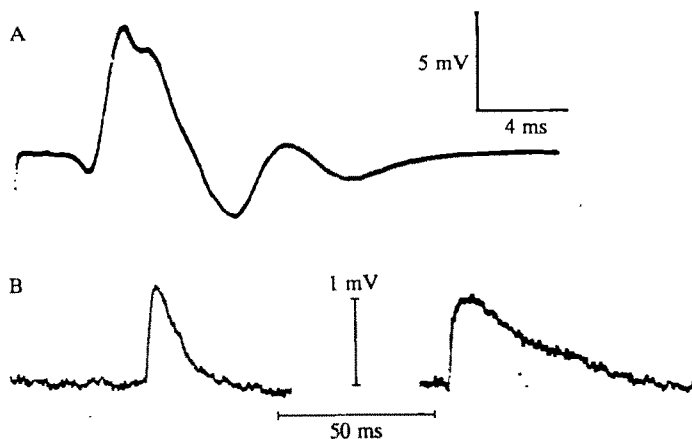


FIG. 4. A, repetitive CMAP in ADM evoked by single stimulus to ulnar nerve at wrist in *Case 1*. B, mepps recorded in biopsied intercostal muscle from a control subject (*left*) and from *Case 1* (*right*).

including biceps, where no decrement was seen. The repetitive response occurred 7 to 10 ms after the first, and was always smaller; it decreased in size at 3 Hz stimuli and after a period of voluntary contractions. Single fibre EMG (EDC) showed abnormal jitter and blockings in 3 of 10 potentials, and abnormal jitter without blockings in 4 potentials. Motor and sensory nerve conduction was normal. Concentric needle sampling showed a myopathic pattern with polyphasic small amplitude motor unit potentials. No fibrillation potentials or positive sharp waves were observed.

### Electrophysiology

Results are shown in Table 2, together with values for control muscles. In controls, the resting potential was  $67 \pm 3$  mV ( $n=6$  endplates) while for Case 1 it was  $65 \pm 4$  mV ( $n=4$ ) and  $77 \pm 4$  mV ( $n=8$ ) with and without physostigmine, respectively. For Case 1, there was a significant increase in both the mepp rise time ( $P<0.02$ ) and the mepp decay time constant ( $P<0.001$ ), the latter being 4 to 5 times control value (fig. 4B). The mepp amplitude and mepp frequency were not significantly different from controls. In the presence of physostigmine, for this patient's muscle, the mepp amplitude was increased somewhat ( $P<0.05$ ), the decay time was significantly increased ( $P<0.002$ ), while the rise time was not significantly affected.

TABLE 2. ELECTROPHYSIOLOGICAL FINDINGS IN INTERCOSTAL MUSCLE BIOPSIES

|                                     | Control                          | Case 1                                                  | Case 2                                                            | Father of Case 2                                        |
|-------------------------------------|----------------------------------|---------------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------|
| Mepp amplitude (mV) <sup>f</sup>    | $1.03 \pm 0.07$ (4)              | $0.84 \pm 0.09$ (8)<br>$1.32 \pm 0.25$ (4) <sup>a</sup> | $0.73 \pm 0.14$ (5)<br>$0.68 \pm 0.08$ (4) <sup>b</sup>           | $0.69 \pm 0.10$ (8)<br>$1.16 \pm 0.11$ (8) <sup>b</sup> |
| Mepp frequency (s <sup>-1</sup> )   | $0.11 \pm 0.07$ (4)              | $0.05 \pm 0.01$ (8)<br>$0.07 \pm 0.01$ (4) <sup>a</sup> | $2.2 \pm 1.5$ (4) <sup>c</sup><br>$0.6 \pm 0.33$ (6) <sup>b</sup> | $0.4 \pm 0.18$ (8)<br>$0.2 \pm 0.02$ (8) <sup>b</sup>   |
| Mepp rise time (ms)                 | $1.2 \pm 0.2$ (4)                | $3.1 \pm 0.4$ (8)<br>$2.0 \pm 0.2$ (4) <sup>a</sup>     | $1.6 \pm 0.4$ (5)<br>$1.3 \pm 0.3$ (4) <sup>b</sup>               | $2.2 \pm 0.5$ (8)<br>$1.5 \pm 0.1$ (8) <sup>b</sup>     |
| Mepp decay time constant (ms)       | $5.7 \pm 0.3$ (4)                | $20.7 \pm 0.5$ (8)<br>$28.1 \pm 2.2$ (4) <sup>a</sup>   | $25 \pm 3.1$ (5)<br>$25 \pm 1.9$ (4) <sup>b</sup>                 | $24 \pm 2.4$ (8)<br>$24 \pm 1.2$ (8) <sup>b</sup>       |
| ACh-induced depolarization* (mV)    | $12.5 \pm 0.8$ (2) <sup>c</sup>  | $15.2 \pm 5.4$ (2) <sup>d</sup>                         |                                                                   |                                                         |
| Single channel depolarization* (μV) | $0.20 \pm 0.03$ (2) <sup>c</sup> | $0.29 \pm 0.13$ (2) <sup>d</sup>                        |                                                                   |                                                         |
| Voltage noise time constant* (ms)   | $6.1 \pm 1.8$ (2) <sup>c</sup>   | $11.4 \pm 1.8$ (2) <sup>d</sup>                         |                                                                   |                                                         |

Means  $\pm$  SE with number of endplates in parentheses. <sup>a</sup> 3  $\mu$ M physostigmine; <sup>b</sup> 3.3  $\mu$ M neostigmine; <sup>c</sup> 1.1–1.3  $\mu$ M ACh; <sup>d</sup> 1.4  $\mu$ M ACh. <sup>e</sup> One endplate showed 21 mepps s<sup>-1</sup> (this value was not used in the table). <sup>f</sup> Corrected to a standard resting potential of -80 mV (assuming an equilibrium potential for the transmitter of 0 mV, Cull-Candy *et al.*, 1979).

The depolarization produced by ACh ( $1.1\text{--}1.4\mu\text{M}$ ) applied in the bath was similar in two endplates to that produced in controls (*see* Table 2). From the voltage noise during these ACh applications it was calculated that the depolarization (*a*) produced by a single channel opening was slightly increased (though not significantly) in Case 1 compared with control values (Table 2). Analysis of the power spectrum of the voltage noise yielded a noise time constant which was higher in the patient compared with control values, although this did not reach statistical significance for the limited available data.

#### *Acetylcholinesterase staining*

Some muscle fibres had normal acetylcholinesterase staining of the endplates, but many fibres showed several discrete patches of stain over 2 to 3 times the normal length.

#### *Alpha-bungarotoxin binding*

The number of toxin binding sites per endplate was  $0.7 \pm 0.1 \times 10^7$  ( $n = 6$  bundles); controls  $1.6 \pm 0.1$ , ( $n = 10$ ; *see* Ito *et al.*, 1978). These results indicate a reduction in the overall number of AChRs.

### *Case 2*

#### *Electromyography*

A decremental EMG response of the CMAP at 3 Hz stimulation was observed in small hand muscles of this patient, and also in her father. A significant decrease of the CMAP was also found in her and her brother by the double step stimulation test (Desmedt and Borenstein, 1977). A single supramaximal stimulus caused a repetitive CMAP, and also in her father and brother. The repetitive CMAP occurred 5 to 18 ms after the first and its amplitude was always smaller; it varied considerably in different muscles of the same patient and was not present in all the muscles tested. The amplitude of the repetitive CMAP was larger and its latency was longer at lower muscle temperatures. For example, the amplitude of the repetitive CMAP of APB was 70% of the first at a skin temperature over the muscle of  $26^\circ\text{C}$ , and 25% at a skin temperature of  $33^\circ\text{C}$ .

Two supramaximal stimuli 1 ms apart each evoked a similar repetitive CMAP. This implies that the repetitive CMAP is not caused by an axon reflex, which would have been blocked by the second stimulus. At stimulation frequencies above 0.2 Hz, the amplitude of the repetitive (second) CMAP decreased, as is clearly demonstrated at a skin temperature of  $26^\circ\text{C}$  (fig. 5). The decrement was more prominent at higher skin temperatures. In addition, posttetanic potentiation was demonstrated both for the initial and for the repetitive CMAP 2 min after a stimulus train at 100 Hz for 10 s. The amplitude of the repetitive CMAP did not change during 12 min of ischaemia and in the period thereafter. Motor nerve conduction velocities were normal. Needle EMG sampling showed a 'myopathic' pattern with polyphasic

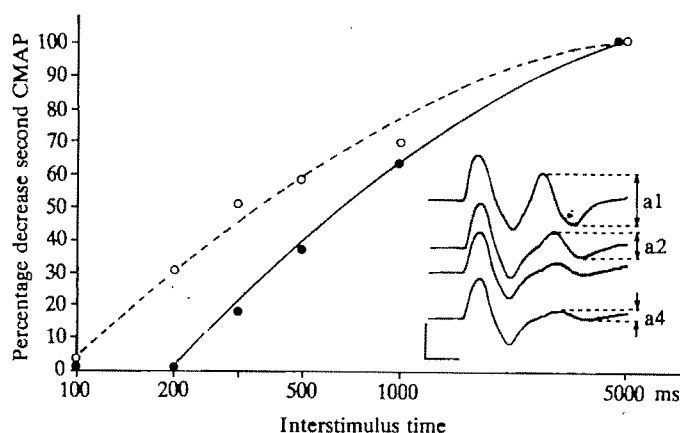


FIG. 5. Amplitude changes of the repetitive (second) CMAP after the second and fourth stimulus as a percentage of that after the first stimulus in *Case 2*.

$$\circ = \frac{a_2}{a_1} \times 100\%; \quad \bullet = \frac{a_4}{a_1} \times 100\%$$

*Inset.* Successive recordings of the first four CMAPs at 3 Hz stimulation in *Case 2*. Recording (surface electrodes) from APB; stimulation median nerve at the wrist; skin temperature over the muscle 26°C. Bars = 5 mV and 5 ms.

small amplitude motor unit potentials. No fibrillation potentials or positive sharp waves were observed.

### Electrophysiology

The resting potential was  $-61 \pm 5$  mV ( $n=5$  endplates) and  $-57 \pm 3$  mV ( $n=6$ ) with and without neostigmine, respectively, while for the father of *Case 2* these values were  $-64 \pm 2$  mV ( $n=8$ ) and  $-62 \pm 2$  mV ( $n=8$ ). As in *Case 1*, the most conspicuous finding was that the decay time constant (Table 2) of the mepps was increased (25 ms). By contrast with the results in *Case 1*, in which physostigmine was used, the decay time constants of the mepps of *Case 2* and her father were not increased after the addition of neostigmine. Although it cannot be excluded that the anticholinesterases physostigmine and neostigmine had different actions on the time constant, it seems more likely that a genuine effect of neostigmine on the time constant in *Case 2* and her father was masked by the variation of the results (Table 2). The rise time of the mepps was somewhat greater than that of controls, but the difference was not statistically significant. The amplitude of the mepps was slightly decreased but within normal limits (Ito *et al.*, 1978). The mepp frequency was relatively high and also highly variable. The reason for this was unclear. In the father the various parameters (Table 2) of the mepps were almost the same as in his daughter except for the mepp frequency, which was smaller. The decay time of the miniature endplate current (mepc), measured under voltage clamp conditions, was increased from  $1.7 \pm 0.1$  ms (Cull-Candy *et al.*, 1979) to 13, 10 and 8 ms in one endplate and 15, 20 and 19 ms in another, and to 18 ms in the presence of neo-

stigmine in a third endplate. (In the daughter there was also an indication of mepps of long duration but in this case the endplates were not well clamped.)

### *Histopathological studies*

*Light microscopy.* No abnormalities in muscle fibres were seen. Histochemical examination revealed a type I fibre preponderance with only 30% type II fibres. Type I fibres were, in general, somewhat smaller than type II fibres.

Intramuscular nerve fibres showed no abnormalities. Preterminal and terminal axon branches were not quantified, but no evidence of abnormal sprouting was seen.

Acetylcholinesterase (AChE) was present at the motor endplates, which were elongated in size and shape. AChR staining in endplate regions was positive. Von Kossa and Alizarin red S staining did not reveal any calcium deposits at endplates or in underlying muscle fibre regions.

*Electron microscopy.* Morphometric analysis of 53 neuromuscular junctions (NMJs) in the patient's biopsy and 18 NMJs in external intercostal muscle of a control patient of the same age was performed as described previously (Smit *et al.*, 1984) (See Table 3). Marked ultrastructural abnormalities contrasted with the almost normal light microscopic findings, the most conspicuous being degeneration and atrophy of junctional folds.

TABLE 3. MORPHOMETRIC ANALYSIS<sup>a</sup>

| <i>External intercostal muscle</i>                                                     | <i>Control</i>    | <i>Case 2</i>       |
|----------------------------------------------------------------------------------------|-------------------|---------------------|
| Neuromuscular junctions analysed                                                       | 18                | 53                  |
| Nerve terminal area ( $\mu\text{m}^2$ )                                                | $2.32 \pm 1.64$   | $2.78 \pm 2.00$     |
| Presynaptic membrane length ( $\mu\text{m}$ )                                          | $3.69 \pm 1.04$   | $3.18 \pm 1.92$     |
| Nerve terminal circumference ( $\mu\text{m}$ )                                         | $6.78 \pm 2.43$   | $7.95 \pm 3.80$     |
| Ratio $\frac{\text{presynaptic membrane length}}{\text{nerve terminal circumference}}$ | $0.57 \pm 0.11$   | $0.40 \pm 0.14^c$   |
| Postsynaptic area of clefts and folds ( $\mu\text{m}^2$ )                              | $8.43 \pm 3.86$   | $6.28 \pm 3.68^d$   |
| Postsynaptic membrane length ( $\mu\text{m}$ )                                         | $53.90 \pm 24.96$ | $34.62 \pm 20.93^e$ |
| Postsynaptic membrane density <sup>b</sup> ( $1/\mu\text{m}$ )                         | $6.40 \pm 0.67$   | $5.75 \pm 1.16^f$   |

<sup>a</sup> Mean values  $\pm$  SD. <sup>b</sup> Ratio of postsynaptic membrane length to area of clefts and folds per nerve terminal. <sup>c-f</sup> Significantly different from control: <sup>c</sup>  $P=0.0002$ ; <sup>d</sup>  $P=0.02$ ; <sup>e</sup>  $P=0.0004$ ; <sup>f</sup>  $P=0.002$ .

The postsynaptic folds were irregularly shaped and often very slender, causing widening of the secondary clefts. Degeneration of the crests of the folds sometimes resulted in a focal widening of the primary synaptic cleft (figs 6–9). Pinocytic vesicles were present in the folds but were not obviously increased in number. Areas of degenerating folds often extended far beyond the borders of many NMJs and were not covered by Schwann cells (fig. 6). The basal lamina covering these regions was diffusely thickened and contained granular material (figs 6–9A). Similar gran-

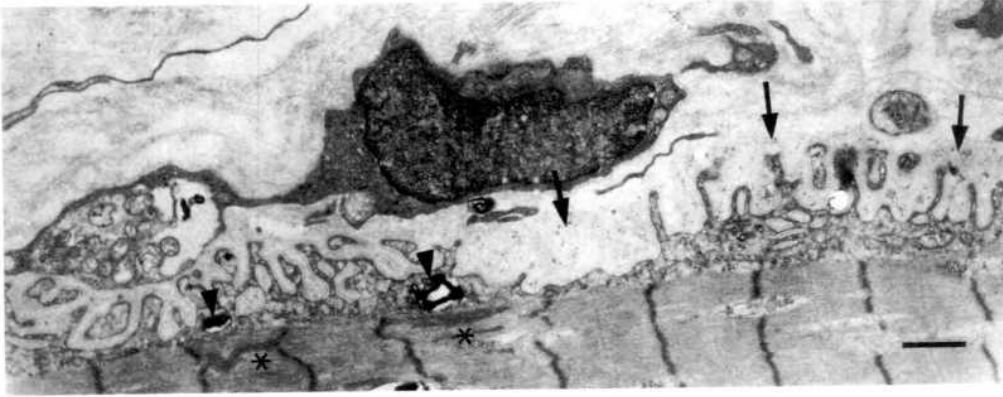


FIG. 6. Electron micrograph of external intercostal muscle from *Case 2*. Degenerated junctional folds extend far beyond the neuromuscular junction, at the extreme left. There is local widening of the synaptic cleft due to degeneration of junctional folds. Granular material is present in the diffusely thickened basal lamina (arrows), and myelinoid figures (arrowheads) in the junctional sarcoplasm. Focal streaming of Z lines (asterisks) is seen in the muscle fibre. Only a few mitochondria are present. Bar = 1  $\mu$ m.

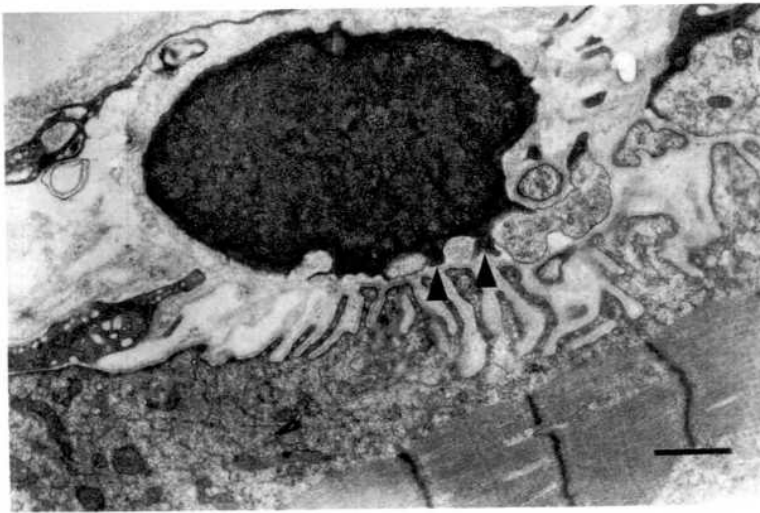


FIG. 7. Electron micrograph. Same biopsy as in fig. 6. Postsynaptic folds are degenerated at some places causing focal widening of the primary and secondary clefts. The nerve terminal is invaded by Schwann cell processes (arrowheads). Bar = 1  $\mu$ m.

ules were also present in normal secondary clefts. Empty holes, possibly reflecting sites originally containing calcium deposits, and deposits with high electron density, probably containing calcium, were frequently observed within this diffusely thickened basal lamina (fig. 9A). Muscle fibres outside the motor endplate regions possessed a basal lamina of normal thickness and appearance (fig. 9A).

Elongated cell profiles could be seen beneath a usually thickened basal lamina (fig. 9A) close to the endplate in 40% of endplates examined. The basal lamina

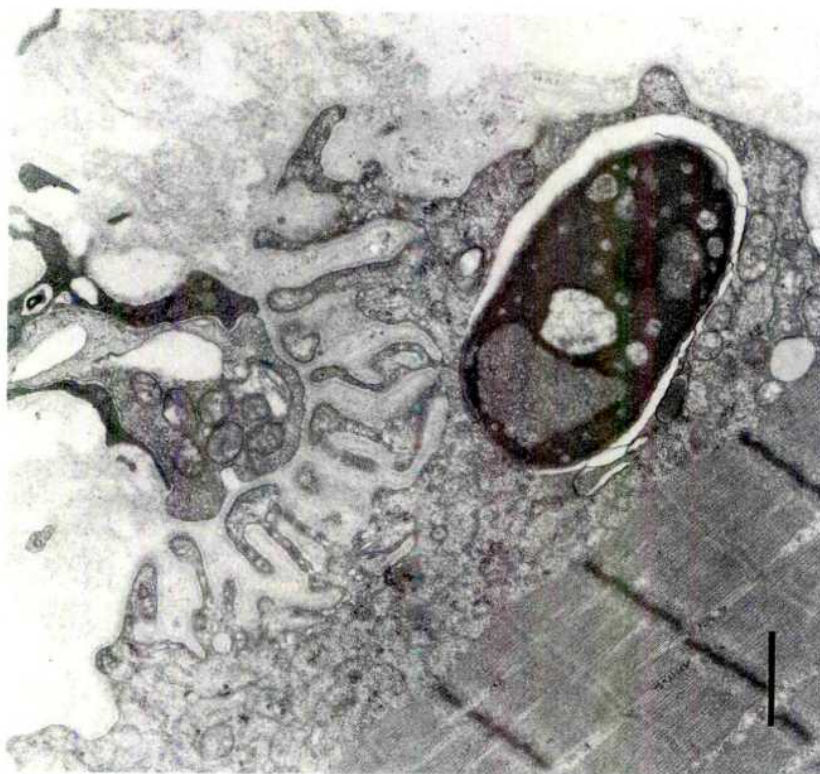


FIG. 8. Electron micrograph. Same biopsy as in figs 6 and 7. The nucleus in the junctional sarcoplasm is degenerated. Widened endoplasmic reticulum is present in the nerve terminal. Bar = 1  $\mu$ m.

covering the muscle fibres was continuous over these cells and did not split to enwrap them (fig. 9B). Parts of these cells were separated by a 20 to 50 nm space from the muscle fibre, and some basal lamina substance was probably present within this space. Delicate processes of such cells sometimes intruded on the underlying sarcoplasm (fig. 9B). The nerve terminals had a normal aspect, whereas Schwann cell processes were occasionally seen to extend between the presynaptic membrane of the nerve terminal and the postsynaptic folds (fig. 7). The synaptic vesicles were abundantly present in some nerve terminals but rare in others, and had a normal appearance.

The junctional sarcoplasm contained some small autophagic vacuoles and myelinoid bodies and occasionally a degenerating nucleus (fig. 8). A minor degree of Z-disc streaming was seen underlying 50% of the NMJs (fig. 6). The NMJs of the control subject were regarded as being normal; only once was a cell profile seen below the muscle fibre basal lamina, in close proximity to an NMJ.

*Quantitative investigations.* A significant reduction in postsynaptic membrane length, the postsynaptic area of clefts and folds, and postsynaptic membrane density was apparent (Table 3). Nerve terminal dimensions were not significantly



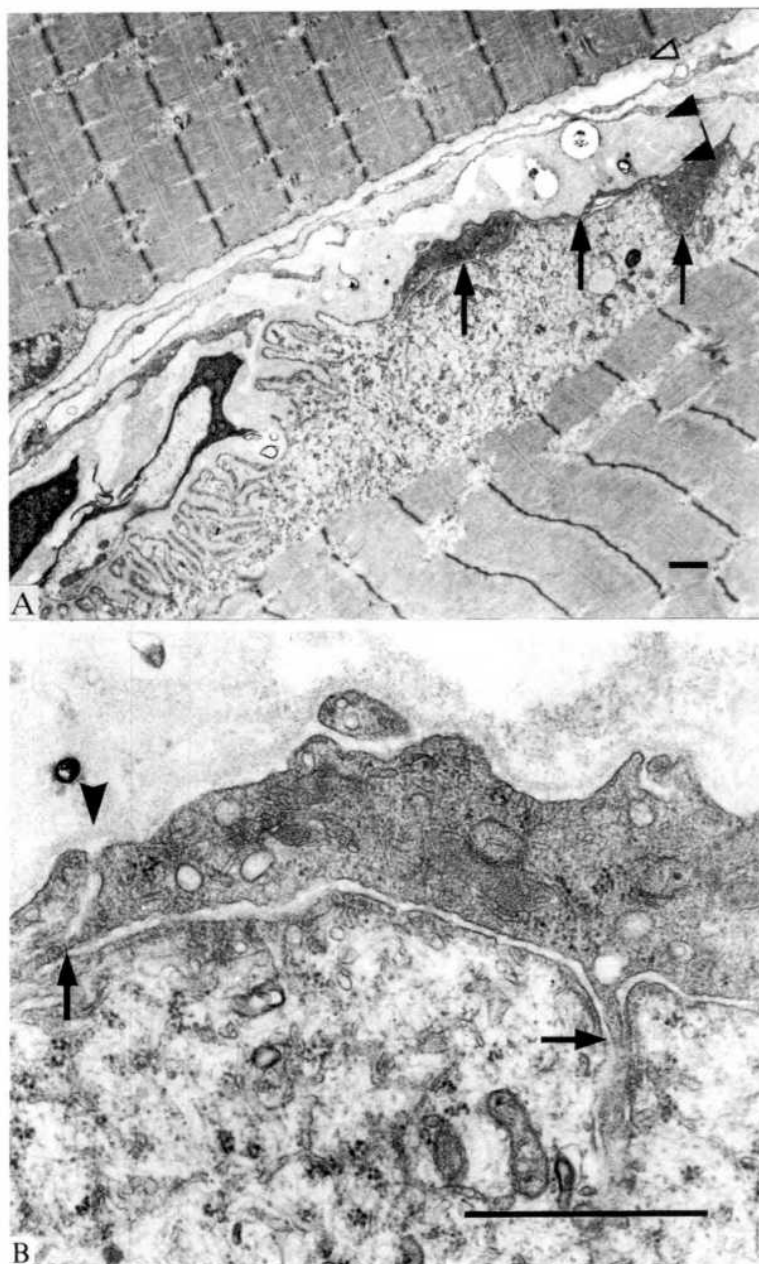


FIG. 9. Electron micrograph. Same biopsy as in figs 6-8. A, the basal lamina in the perijunctional region is diffusely thickened (double arrowhead) and contains empty holes. Some holes are partly filled with material of high electron density suggesting calcium deposits. There are three perisynaptic cells to the right of the junction (arrows). The opposite muscle fibre has a normal basal lamina (open arrow head). B, detail of the perisynaptic cell bordering the neuromuscular junction. Muscle fibre basal lamina is continuous over this cell (arrowhead), which is separated from the muscle fibre by a 20-50 nm space. Delicate processes intrude upon the junctional sarcoplasm (arrows). Bars = 1  $\mu$ m.



TABLE 4. CLINICAL FEATURES OF THE SLOW CHANNEL SYNDROME

|                                          | <i>Engel's patients</i> |          |          |          |          |          | <i>Our patients</i> |          |
|------------------------------------------|-------------------------|----------|----------|----------|----------|----------|---------------------|----------|
|                                          | <i>1</i>                | <i>2</i> | <i>3</i> | <i>4</i> | <i>5</i> | <i>6</i> | <i>1</i>            | <i>2</i> |
| Sex                                      | M                       | M        | M        | M        | M        | M        | W                   | W        |
| Age at onset (yrs)                       | Inf.                    | Inf.     | Inf.     | 20       | 12       | Inf.     | 23                  | 21(16)   |
| Age at examination (yrs)                 | 32                      | 12       | 34       | 54       | 29       | 48       | 28                  | 24       |
| Familial incidence                       | +                       | +        | —        | +        | +        | +        | —                   | +        |
| Ophthalmoparesis                         | +                       | +        | —        | +        | +        | +        | —                   | —        |
| Ptosis                                   | —                       | —        | —        | ±        | —        | +        | —                   | +        |
| Neck muscle weakness                     | +                       | +        | +        | +        | —        | +        | +                   | —        |
| Bulbar weakness                          | ±                       | ±        | ±        | 0        | —        | +        | —                   | —        |
| Arm muscle weakness                      | +                       | +        | +        | +        | +        | +        | +                   | ±        |
| Leg muscle weakness                      | +                       | +        | —        | —        | —        | —        | +                   | ±        |
| Respiratory weakness                     | +                       | —        | —        | —        | —        | —        | —                   | —        |
| Muscle atrophy                           | +                       | —        | ±        | +        | +        | ±        | ±                   | —        |
| Fatiguability                            | +                       | 0        | 0        | +        | +        | 0        | +                   | +        |
| Effect of anticholinesterases            | —                       | 0        | —        | 0        | 0        | 0        | —                   | —        |
| Hypersensitivity to anti-cholinesterases | +                       | 0        | +        | 0        | 0        | 0        | +                   | —        |
| Effect of prednisone                     | —                       | 0        | —        | 0        | 0        | 0        | —                   | 0        |
| Repetitive response                      | +                       | 0        | +        | +        | +        | +        | +                   | +        |

Inf = infancy; + = present; ± = mild; — = absent; 0 = not stated/not examined.

changed but the ratio of presynaptic membrane length to nerve terminal circumference was significantly decreased. The extent to which nerve terminals were surrounded by Schwann cells was increased.

## DISCUSSION

Our two cases showed clinical similarities to the cases reported by Engel *et al.* (1982). Although the pattern of motor involvement was variable in their patients and ours, all had arm weakness and all but two had neck weakness (Table 4). Fatiguability was a common symptom and was defined by quantified tests in our cases. Onset of symptoms was in adolescence or in early adult life in both our cases, as in 2 of theirs. In both groups, there were cases of apparently autosomal dominant inheritance and a sporadic case. A further feature, common to all patients who were tested, was the absence of improvement with edrophonium or pyridostigmine and some had clinical signs of hypersensitivity to these drugs. However, our patients were different from theirs in the absence of muscle atrophy, except the mild atrophy of the hand muscles in Case 1. CT scans of the proximal muscles were also normal.

Both our patients, and the 5 cases tested by Engel *et al.* (1982), showed a repetitive response to a single shock and decrement was observed in clinically affected muscles. Although no weakness or fatiguability was present in the father and brother of

Case 2, a repetitive CMAP and an abnormal decrement were demonstrable in both of them. This indicates that these abnormalities are not always confined to clinically weak muscles, confirming the observations of Engel *et al.* (1982).

The difficulties in reaching the correct diagnosis in these patients need stressing. Our patients presented with symptoms and signs that raised the suspicion of acquired autoimmune myasthenia gravis. In the first patient, obvious fatigability and the decrement at slow rates of supramaximal nerve stimulation seemed to favour the diagnosis. She also had a 'typical' onset at the end of pregnancy with a short remission and a relapse several weeks later. However, the absence of serum anti-AChR antibodies (detectable in about 90% of patients with generalized MG) and the adverse reaction to anticholinesterase drugs led to a review of the diagnosis. The patients reported by Engel *et al.* (1982) also had clinical features that suggested diagnoses other than myasthenia and in fact led to an initial diagnosis of a primary myopathy in some cases. The important diagnostic finding is the repetitive response to a single stimulus, which was present in both patients, and which also enabled a subclinical abnormality to be detected in the father and brother of Case 2. This repetitive response is easily overlooked if 3 Hz stimulation is used without display of the CMAP on a long time base. In addition, as Engel *et al.* (1982) have pointed out, the repetitive response is absent after a short voluntary contraction. We also found that the amplitude of the repetitive response decreased rapidly at higher frequencies but did not decrease at 0.2 Hz stimulation. This latter finding is useful in distinguishing the repetitive response from artefact, and its routine use is recommended in investigating atypical cases of myasthenia.

In both patients and the father of Case 2, the mepp amplitude, which is the depolarization resulting from the release of a single packet of ACh, was normal, but the time course of the depolarization was significantly slowed. The rise time of mepps is partly dependent on the positioning of the microelectrode in relation to the endplate, and in normal tissue a slow rise time would be associated with reduced amplitude indicating that the electrode was too far from the site of the depolarization. However, in these patients' muscles the amplitude was normal, suggesting that the slow rise time observed in Case 1 was not due to malpositioning of the electrode.

The slowed rise time and lengthened decay constants of the mepps are most likely to be due to an increase in the length of time each channel stays open. In human intercostal muscle the mepp arises from the almost simultaneous opening of a few thousand ion channels (Cull-Candy *et al.*, 1979), each of which normally produces a depolarization of 0.2 to 0.3  $\mu$ V with a decay constant of about 6 ms (Table 2). The contribution of these elementary events was analysed by measuring voltage noise during the application of ACh. Limited data on Case 1 indicate that the single channel depolarization was slightly higher and the decay time was prolonged. This effect could be explained by an increased open time of the channel. Alternative explanations for the slowed rise time include the abnormal geometry of the synaptic space, and the effects of the thick basal lamina which may hinder

ACh diffusion. A further explanation can probably be excluded, namely an increase in membrane time constant without change in channel open time. In normal muscle the decay of the single channel depolarization mainly depends on the membrane time constant which determines the passive decay of charge resulting from the opening of the channels. If the membrane time constant was increased, then the decay time constant of both the single channel depolarization and the mepp would be prolonged. In that case, however, the rise time of the mepps would hardly be affected, and the single channel depolarization would be considerably reduced. Since in Case 1 the rise time was prolonged and the single channel depolarization was within normal range or even increased, an increase in the membrane time constant is highly unlikely. For Case 2 and her father, the decay time constant of mepcs was increased. Because the time constant for decay of mepcs is usually similar to channel open time (in the absence of AChE inhibition), the increase in mepc decay time in Case 2 is likely to be due to an increase in channel open time (Anderson and Stevens, 1973). Alternatively, if the presence of ACh in the cleft is prolonged by the absence of AChE, this would also cause prolongation in the mepc decay. However, we found no evidence for AChE deficiency.

The repetitive CMAP evoked by a single supramaximal nerve stimulation can be explained by the long duration of the epp caused by the abnormally long duration of the elementary events. Thus the prolonged epp triggers a repetitive action potential if the epp amplitude remains above threshold during a period longer than the refractory period of the muscle fibre. This presumably occurs in only a fraction of the muscle fibres since the repetitive CMAP is of lower amplitude than the first. Epps would be expected to be even more prolonged at low temperatures, causing a further increase in amplitude of the repetitive firing, which was indeed observed. Interestingly each nerve stimulus produced only a single repetitive discharge, in contrast to cases we have studied with excess anticholinesterase medication, where as many as four CMAPs of decreasing amplitude may follow a single stimulus.

The main feature of the ultrastructural changes, demonstrated in our second patient, was degeneration of junctional folds and in this regard our findings were identical to those of Engel *et al.* (1982). Other points of similarity were the presence of degenerated folds next to NMJs, granular debris in the basal lamina substance and increased Schwann cells surrounding the nerve terminals. There were also some differences: (1) the myopathic changes in our patient were less prominent; (2) there was no diminution of nerve terminal size; and (3) endplate basal lamina was diffusely thickened.

It has been suggested that the damage to the junctional folds and their underlying sarcoplasm is the consequence of an increased calcium influx which is made possible by the prolonged open time of the ACh-induced ion channel (Engel *et al.*, 1982). The observations that calcium deposits were only demonstrated at the ultrastructural level, that only a few myopathic changes were present in our patient, and that the nerve terminal size was preserved, point to a lesser degree of involvement of

the external intercostal muscle neuromuscular junctions in comparison with those examined by Engel *et al.* (1982).

An increase in the degree to which the Schwann cell surrounds the nerve terminals may follow any disorder that leads to a decrease of ACh effect, but it is also seen in the AChE deficiency syndrome (Engel *et al.*, 1977).

Areas with degenerated folds close to many of the NMJs were seen in other cases of the slow channel syndrome, and described as 'denuded' by Engel *et al.* (1982), implying that they are denervated endplate areas. If this interpretation is correct, it must be assumed that the nerve terminal and its Schwann cell retracts from the damaged postsynaptic membrane and forms a new junction close to the original one. This could be responsible for the observed elongation and patchiness of AChE staining.

The diffuse thickening of the endplate basal lamina substance is not described as a prominent finding in the cases of Engel *et al.* (1982), in the AChE deficiency syndrome (Engel *et al.*, 1977), or after chronic treatment with acetylcholinesterase inhibitors (Hudson *et al.*, 1978). In MG, layered basal lamina has been observed over damaged endplates (Sahashi *et al.*, 1980). A comparable degree of endplate basal lamina thickening is absent in the Eaton-Lambert syndrome (Santa *et al.*, 1972), in one other form of congenital myasthenia (Smit *et al.*, 1984) and after denervation by nerve section or colchicine treatment (Gonzenbach and Waser, 1973; Pulliam and April, 1979*a, b*; Pachter and Eberstein, 1983). It is of interest that in our first patient, relatively high AChE activity was present in the endplate regions under light microscopy. AChE is attached to endplate basal lamina and is probably synthesized by the muscle fibre, but neural mechanisms may have a regulating influence (McMahan *et al.*, 1978; Sanes and Chiu, 1983).

The presence of perisynaptic cells which are covered by muscle fibre basal lamina has not previously been described in human endplates (Chou, 1982). The nature and origin of these cells is at present not definitely established. Perisynaptic satellite cells have been described in endplates of the rat soleus muscle (Kelly, 1978; Cardasis, 1983). The existence of a 20 to 60 nm space between satellite cells and the muscle fibre, which may be partly filled with basal lamina substance, has been observed in endplates (Cardasis, 1983) and elsewhere along the muscle fibre in ageing (Snow, 1977) and after denervation (Schultz, 1978).

It appears that the long duration of the epps, although apparently the basic abnormality in the disease, is not of itself the direct cause of the weakness, as indicated by the results of the father of Case 2. Morphological changes seem more likely to be responsible, for instance if they interfered with the initiation of the muscle action potential. An alternative possibility, not excluded by the present results, is that the number of ACh packages released by the nerve impulse is decreased, particularly in severely affected muscles.

The sharing of some clinical features between our cases and those of Engel *et al.* (1982), taken together with the electrophysiological findings, particularly in Case 1, suggests that the disorder in the two groups of patients has a similar cause. This

is likely to include a prolonged open time of the ACh-induced ion channel. Some of the observed clinical differences could be explained by the time required for the functional disorder to lead to permanent weakness and atrophy.

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## BOOK REVIEWS

### **A Manual of Diseases of the Nervous System.** By W. R. Gowers

This year is the centenary of the publication of *A Manual of Diseases of the Nervous System* by Sir William Gowers. It was suggested to us by Dr Malvin Cole that the occasion should not pass unnoticed. We are therefore reproducing the review of the book that was published in *Brain*, Volume 11, 131–133, and which was written by Dr A. de Wetteville, editor of *Brain* at the time, together with a commentary provided for us by Dr R. A. Henson, deputy editor of *Brain* from 1974–1981. It may be of interest to cite an extract from a letter from Weir Mitchell to Gowers congratulating him on his knighthood at the Diamond Jubilee of Queen Victoria which reads ‘... Your book on nervous disease stands for us all as the best of many great textbooks—it has been the rich mine from which the material for many treatises has been taken—it is the book to which I turn first when my own knowledge fails...’. (McDonald, 1986).

**A Manual of the Diseases of the Nervous System.** By W. R. Gowers MD, FRS. 2 vols. 8vo, 463 and 975 pp. 370 figs. Churchill, London, 1886–1888.

The first instalment of this work, containing the Diseases of the Spinal Cord and Nerves, is no doubt already familiar to many of our readers; but we are glad that the publication of the second—more important, as well as voluminous—gives us an opportunity of noticing the work as a whole. We must, however, deny ourselves the pleasure of writing at any length concerning Dr Gowers’ volumes; for they belong to the category of works indispensable to those interested in Neurology, upon whose shelves they will speedily occupy a conspicuous position. Their contents, moreover, are so vast as to make it impossible in a review to enumerate the subjects handled by the author, far less to attempt an analysis and discussion of the views held by him on the numerous problems with which he has to deal. We shall limit ourselves, therefore, almost entirely to a statement of the leading features of this manual, that characterise it as one of the very best published in any language.

What we admire, first, is the clearness of thought and language in the exposition, even in the more difficult portions of the subject. It is not every one who being a master, is at the same time a skilful expounder, and knows how to elucidate, whilst condensing, his theme. Secondly, we find the evidence, on every page of the book, of the author’s individual familiarity with the topics he is discussing. Dr Gowers’ work in this respect often partakes of the interesting freshness of an original treatise, such is the wealth of personal information woven into his exposition of the subject in hand. Finally, we note the thorough mastery of the author of the most recent researches: a most creditable accomplishment when one considers the disproportion between the time at the disposal of a London physician in full practice, and the wealth of our contemporary neurological literature. Nor are the chapters devoted to the scientific or theoretical aspects of neuropathology the only ones deserving praise; those devoted to the practical aspect of the question, to nerve-therapeutics—this too often neglected ‘partie honteuse’ of our branch of medicine—will be found if not always sanguine and cheerful, at least earnest and suggestive. Readers of French and German works on nervous diseases will however notice the larger share of attention given by Dr Gowers, in common with most English authorities, to internal medication as compared with that bestowed upon hydrotherapeutics, massage, active and passive movements, and the like, under the various headings of treatment.

The Manual contains accounts not only of the leading morbid types, but of numerous minor

forms of nerve disturbance, many of them to be found mentioned only in quite recent papers and monographs; and its interest and value are thereby enhanced for the professed neurologist, as much as for the student and general physician. Dr Gowers would, however, add still further to our debt of gratitude to him as a guide through the field of neuropathology if, in his next edition, he were to give us a chapter of the pathology and treatment of stammering, a subject too much left to the 'exploitation' of empirics. Morphinism might advantageously be adverted to under the heading of intoxications; and perhaps a sketch of the leading symptoms of general paralysis would be useful, especially in connection with certain phases of tabes. Another item which we miss in the present volumes is an index to the figures, many of which are very instructive. These suggestions, however, hardly deserve the name of criticisms. So in order not to derogate to the time-honoured tradition of reviewers always to find some fault with the work under notice, we shall attract Dr Gowers' attention to some verbal mistakes in the course of the book. Thus, for instance, on p. 104 we find 'Sepelli' for Seppili, 'die' for 'der' Complex; p. 924, the French expression for pleurosthotonos should be 'arc de cercle latéral,' &c. &c. But these are minor points. We find that Dr Gowers adopts the absurd 'pontine' for 'pontal.' Pontine is the name of marshes near Rome, but not the adjective derived from pons. Again, as the Greek 'method' gives 'methodic,' so anōd and kathōd (usually misspelt and mispronounced anōde and kathōde) give anōdic and kathōdic, not anōdal and kathōdal. Again 'faradaic,' is not only pedantic but inexact: in forming an adjective from the name Faraday, the terminal diphthong *ay* should be replaced by the termination *ic*. With reference to the expression *myotatic*, introduced to designate the nature of the phenomena of tendon excitability known as knee-jerk, &c., we think (after some hesitation, we must confess) that it is a useful one, and deserving to be generally adopted.

A. DE WATTEVILLE

*Commentary by Dr R. A. Henson*

The task of the conscientious reviewer is difficult. According to George Lyttelton (1978), he should take trouble to discover what the author was trying to do and to formulate a clear notion of the nature and extent of the problems confronted. Never once should he draw attention to himself or to how much cleverer he is than the hoi polloi. Landor put the matter succinctly, 'we admire by tradition and criticise by caprice'.

De Watteville's review offended Gowers (Critchley, 1949). Reading the piece a century later, the first paragraph was warm enough, though the writer shied away from thorough analysis of a major work. Most of the second paragraph was fulsome, but towards the end De Watteville drew attention to himself, first as a linguist and secondly as a proponent of physiotherapy. The third paragraph provided more plausible cause for complaint as the reviewer proceeded to correct Gowers on linguistic grounds. These corrections were justified but 'the absurd pontine for pontal' must have stung. According to Critchley (1949) these 'inappropriate sneers' piqued Gowers and De Watteville was probably never forgiven.

Compared with critiques found in literary and musical journals both then and now, De Watteville's strictures were mild indeed. The juxtaposition of reviewer and reviewed was unfortunate; De Watteville took the task upon himself despite unfavourable auguries, for he must have been aware of Gowers' personal antipathy.

Gowers is remembered as a seminal contributor to British neurology. He was an outstanding clinician, teacher, and observer. In his pious biographical appreciation, Critchley (1949) was concerned with Gowers' contributions to medicine, and there is little to strike a sympathetic spark for Gowers the man. Indeed Critchley used such inimical descriptive terms as cold, arrogant, and withholding praise from his juniors, but Henry Head (1902) found Gowers a congenial companion at Royal Society dinners. The full story of Gowers has not been told, but he was evidently not a man to accept criticism graciously, particularly if it flowed from a disliked source.



Set against this celebrated figure was Armand De Watteville, scion of a distinguished Swiss family, whose credentials as a physician have not been fully documented (Henson, 1978). His qualifications were LRCS and MD (Basel). While De Watteville held several hospital appointments in London none were comparable with those of Gowers. He was a prolific writer and served on the editorial staff of the *British Medical Journal*. His skills as a linguist were deployed in translations of Erb and Charcot, and his honorary membership of four foreign societies indicated international standing. The Neurological Society of London was founded in his house in 1885, and his association with the Society was responsible for his appointment as a somewhat egregious editor of *Brain* in 1888. Gowers was never a member of the Society, largely because of his personal dislike of De Watteville, nor did he publish in *Brain*, for the same reason (Critchley, 1949).

Most romantic of *Brain* editors, De Watteville was certainly the only one with a family regiment. De Watteville's regiment was in British pay during the early Napoleonic wars and was embodied in the British Army in 1801. After active service in several theatres, the formation was disbanded in Canada following the battle at Fort Erie (1816). De Watteville was a colourful figure, known in London as Baron. He had a nice sense of humour and a serious concern for the right use of words. In the aftermath of the Franco-Prussian War of 1870 he was arrested and sentenced to be shot as a communist; fortunately the mistake was discovered and he was freed. An excellent mountaineer, he made the third ascent of the Great Eiger. Gowers and De Watteville were certainly a disparate pair, and the latter may have been trailing his coat in his review.

Turning now to the Manual, with the personal animosities of a century ago forgotten, what can be made of the work? Responding to time-hallowed advice at Queen Square, I acquired volumes 1 and 2 after the last war, but I found them unreadable. The Manual represented neurological history, and there were more pressing concerns for the returning soldier. Today, the elegant, precise language frames Gowers' confident mastery of his subject and reveals his incisive intelligence. His drawings reflect his skill with the pencil (he was also a capable engraver). Period influence is naturally strong, and there is a point where one might be reading Sir Hubert Parry on primitive musics — but I draw attention to myself. The reader is reminded throughout of the neurological darkness obtaining in the 1880s, and Gowers showed himself aware of this.

Drawing on his own experience and clinical acumen, Gowers produced a textbook of remarkable scope for the time. De Watteville hinted delicately at the poverty of references in his review, and this was fair comment. When Gowers strayed beyond his experience the occasional error crept in, as in his assertion that 'hysteria is unknown in barbarous (sic) peoples'. The Manual remains an important source for those interested in the state of British clinical neurology one hundred years ago. After all, the past can still fertilize the present.

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**Stanely Cobb: A Builder of the Modern Neurosciences.** By Benjamin V. White. 1984. Pp. 445. Charlottesville, VA: University Press of Virginia. Price \$29.50.

It is now almost twenty years since Stanley Cobb's death. He was born 100 years ago to an old New England family, grew up in what was then a close-knit society centred on Boston, was particularly interested in biology at Harvard College and graduated from Harvard Medical School in 1914. After a year of surgery with Harvey Cushing, Cobb left Boston for Baltimore where he worked in neurophysiology with William Henry Howell and in psychiatry with Adolph Meyer. After eight months in the Army Medical Corps, he returned to Harvard Medical School in 1919 and soon came to direct its neuropathology laboratory. With support from the Rockefeller Foundation, Cobb spent 1923 to 1925 in Europe where he worked with the Vogts and Bielschowsky in Berlin, Lhermitte and Foix in Paris, Henry Head in London and Sherrington and Fulton in Oxford. He then returned to be Chief of the Neurology Service at Boston City Hospital which he developed into what Penfield called 'the strongest school of contemporary neurology in the United States.' His studies of cerebral circulation, including the demonstration that cerebral vessels are reactive to carbon dioxide rather than oxygen content of blood, were crucial to the development of modern concepts. Cobb's methods were qualitative but until Kety's quantitative analyses, Cobb's studies were the basis of knowledge of cerebral blood flow. Amongst those who were with him, William Lennox did pioneering research in epilepsy, Tracy Putnam and Houston Merritt discovered phenytoin, Harold Wolff studied mechanisms of headache and Frederick Gibbs' demonstrations of the clinical utility of EEG interested Robert Schwab and others in developing it as a routine test. In 1934 Cobb moved to the Massachusetts General Hospital to head the newly created Psychiatry Service which also flourished, attracting more young people who went on to become well known, among them were William Sargant, A. D. Leigh, Mandel Cohen, Eli Robbins, E. P. Richardson and John Nemiah. There was, at that time, a spirit of healthy competitiveness between the Boston City Hospital and the Massachusetts General Hospital; Derek Denny-Brown, Cobb's eventual successor at 'the City' said, 'Stanley was a little naive in his psychiatric thinking. Only he could have introduced psychiatry into the Massachusetts General Hospital'. Nevertheless, treatment of the mentally ill within a general hospital setting was an idea whose time had come. Cobb, after retirement in 1954, had more time for his life-long interest in ornithology; he spent the remainder of his life studying the comparative neuroanatomy of birds. He also witnessed the devastating effects of insecticides and wrote *Death of a Salt Pond*.

These are but the bare bones outlining the curriculum vitae of an important figure on the Boston neurological and psychiatric scene. His career, a most interesting and unique one, is described in considerable detail in the book which is the subject of this review. Written by Cobb's son-in-law, this book began as a family history but eventually developed into a serious biography, requiring a great deal of research by the author. He was helped in this by Cobb's wife and sister as well as by tape-recorded interviews with many of those who had been associated with Cobb. Benjamin White, a physician himself, is clearly a most sympathetic biographer; one might question his objectivity but certainly not his historiographic efforts. Dr White describes Cobb as 'one of the most important and influential teachers, researchers, and practitioners of neurology and psychiatry in America and an important figure world-wide'. Cobb is said to have been responsible for integrating the practice of neurology with psychiatry, for bringing psychiatry into the modern hospital environment and for introducing psychoanalysis into the medical school curriculum. He was trained in human and comparative anatomy, neurophysiology, neuropathology, neurohistology, clinical neurology, and finally psychiatry. Cobb attempted to piece together fragments of these sciences into an understanding of the nervous system that was imaginative and unique. In so doing, he may have added several important building blocks to the foundations of what we now call Neuroscience. Cobb was a monist regarding the mind-body problem and described the brain as the organ of the mind. Also, for better or for worse, he was as responsible as anyone for the ascendancy of analytical psychiatry in Boston and throughout the United States. He was analysed himself and believed in the value of psychoanalysis as an educational tool.

Cobb has been faulted as a polymath or dilettante by others who perhaps failed to understand or appreciate his breadth of vision. They felt he would have achieved more scientifically had he restricted his interests to one discipline, namely theirs. No doubt they were correct but, as an original, his comprehensive view certainly transcended the limited parochialism that characterized and still characterizes medical and scientific specialities. It is obviously difficult to know how Stanley Cobb will be viewed in another hundred years' time. His laboratory work is only cited infrequently in reviews of cerebral blood flow but his influence was always more general anyway. He was, by all accounts, an uncommonly lucid and inspiring teacher with an unusual capacity for sifting through masses of data and organizing the material into clear, concise form. His yearly medical school lectures on neuropathology were well received and the text that grew out of them (*Foundations of Neuropsychiatry*, six editions) made exciting reading for a student interested in the brain.

Perhaps because of all that, he attracted bright young people to work in his department; he also had the invaluable ability to find and bring out the best in those associated with him. While fostering their developments in medical science, he did not subject his colleagues to rigid systems of thought or inflexible routines. He encouraged each of them to find an area of interest to *them* and do what they thought best to make it their own, during which time he supported them wholeheartedly. At the same time, he told them, 'But for God's sake, be tolerant of what the other person is doing.' He was a socially-active, practising Liberal. Cobb was the first to appoint a black physician to the Massachusetts General Hospital house staff, he fought antisemitism in the hospital and university setting, and he actively supported and recognized refugees from Nazi Germany. Cobb's sense of values, his loyalty and concern for his associates' struggles and goals undoubtedly modified and enhanced their careers. There are all too few Chiefs of Service these days who are genuinely interested in what is best for each of their students (as opposed to what is best for Science, for the Chief, or the students' future promotability); there were probably very few like Stanley Cobb fifty years ago either.

Although this book doesn't read like a novel, it is filled with fascinating detail and I recommend it to anyone interested in the history of academic neurology and hospital psychiatry, particularly as viewed from a Boston perspective.

ROBERT R. YOUNG

**Clinics in Immunology and Allergy.** Volume 6, No. 3. AIDS and HIV Infection. Edited by Anthony J. Pinching. 1986. Pp. 687. London: Bailliere Tindall/W. B. Saunders. Price £17.50.

The AIDS epidemic continues and with it, torrents of literature on the subject. It is therefore a great joy to come upon this volume—manual or handbook might be a better description—which in some 250 pages sets the whole topic in perspective for what the guest editor Anthony Pinching calls 'The jobbing clinician with an enquiring mind'.

There are 17 contributors, 8 from the US, 2 from France, and 7 from the UK. The world perspective is therefore given a European or British focus. The information is conveyed in a compact, succinct style with an enviable consistency between contributors; editing and subediting is superb. There are 12 chapters, ranging from the epidemiology of AIDS worldwide, the spectrum of HIV infection, and separate chapters on radiological, virological and immunological aspects, as well as sections on various organs and systems principally involved in HIV infection, pulmonary, gastrointestinal, cutaneous; there is a chapter on central and peripheral nervous system complications of AIDS. Counselling is not forgotten.

One of two statistics indicate what we are up against. In March 1986 there were 18,070 known cases of AIDS in the US, the projection for the doubling time until the next 18,000 cases is 12 to 15 months. In Europe the prevalence of AIDS expressed as per million of population shows strange diversity, 5.1 in the UK, 10.4 in France, 15.4 in Switzerland. In Africa, where reliable data are scarce, in 1983 the estimated prevalence rate in Kinshasa, Zaire, was 38 cases per 100,000 population.

For the neurologist there are 15 pages detailing the opportunistic infections, opportunistic neoplasms, and disorders unique to AIDS (e.g., AIDS dementia complex) and immunopathological injury. Mention is made of retinal lesions in cytomegalovirus infection and the possibility of early treatment with newer drugs (DHPE). So rapid has been the accumulation of papers and reports that the list of spinal cord complications of AIDS is not quite complete. HIV infection as a primary event may produce myelitis which appears to be transient or persistent.

All the chapters have full but not indigestible lists of references; very few are earlier than 1984—a change from the usual reviewer's cry of 'no recent references'.

This report from the front line of the war against AIDS is welcome, timely and, I suspect, will be instantly popular. It deserves to be, not only with 'jobbing clinicians' but with any doctor who has to deal with AIDS and HIV infection, and this includes just about all of us.

HILLAS SMITH

**A Clinicians View of Neuromuscular Diseases.** Second Edition. By Michael H. Brooke. 1986. Pp. 388. Baltimore: Williams and Wilkins. Price £38.00.

The first edition of this book, published ten years ago, was generally well received, despite, or perhaps because of, the idiosyncratic nature of its contents. This second edition retains the same basic plan, consisting of 9 chapters, 8 of which are devoted to descriptions of the clinical features, and to some of the morphological and biochemical aspects of diseases of muscle, the motor end-plate, and the anterior horn cells. The peripheral neuropathies, as in the earlier edition, are omitted and Dr Brooke has little or nothing to say on drug-induced myopathies or other toxic myopathies, end-plate, or anterior horn cell disorders. The book begins with useful practical advice on the examination of patients with neuromuscular diseases, and advice on simple grading systems for use in analysing progressive disorders. The descriptions of individual disorders are generally interesting although there is much that appears to represent Dr Brooke's opinions, rather than referenced observations. This by no means detracts from the book for the educated reader but, for the newcomer to the field there is a danger that received wisdom, and Dr Brooke's wisdom, might be confused. Generally speaking, the book tends to emphasize newly described biochemical aspects of neuromuscular disorders to the loss of the balance of emphasis in the book as a whole. Thus a number of disorders are described in detail although but a few cases have actually been described or recognized. On the other hand, there is a welcome increase in emphasis on the late effects of Duchenne muscular dystrophy, and on manageable aspects of the progressive disorder caused by this disease. Clearly, the recent flood of new information on genetic aspects of this disease is such that this section of the book must inevitably have been out of date within a few weeks of production of the book. The references are placed, as previously, after each disorder described in the text and thus there is a tendency to repetition. The index is astonishingly brief, so much so that it is hardly worth including in the book. This must detract from the usefulness of the volume to the average reader.

MICHAEL SWASH

**Syringobulbia. A Contribution to the Pathophysiology of the Brainstem.** By N. Jonesco-Sisesti. Translated into English, edited and annotated by R. T. Ross. 1986. Pp. 315. New York: Praeger. Price \$49.00.

Students of syringomyelia will be familiar with the name Jonesco-Sisesti for he has been given the eponymous distinction of describing the medullary clefts in such cases. This monograph on 'Syringobulbia' was written in the French language in 1932, and this English edition, published in 1986, follows the translation of the original text by Professor R. T. Ross. Professor Ross comments that syringobulbia is an uncommon disease but its study leads to a better understanding of brainstem

anatomy and physiology. He claims that Jonesco-Sisesti's book is the only comprehensive monograph devoted to the subject.

The book itself comprises a review of the literature of the neuroanatomy of the brainstem and the disturbances created therein by the clefts of syringobulbia. The author maintains that syringobulbia is the bulbar equivalent of syringomyelia and recent investigations have confirmed his belief that the disorder may occur independent of the cervical syrinx or coexist. George Guillain, in his introduction to the 1932 edition, emphasizes the occasional abrupt onset of syringobulbia and the occasional difficulty in differential diagnosis where the patient's symptoms may include sudden vertigo, pain or hiccough. These studies on syringobulbia, which led to the recognition of hitherto unrecognized cell groups. The chapters devoted to the physiology of the vagus nerve and the intermediate nerve of Wrisberg and the vestibular nerve are of particular value. Anatomical descriptions of the lesions of the brainstem in syringobulbia are based on serial microscopic sections. Guillain describes this book as 'a work of art that does the greatest honour to its author'.

The first section of the book is devoted to the modes of onset of syringobulbia, describing those cases mentioned in the literature up to 1932. The author differentiates between those patients suffering an abrupt onset and those whose symptoms are more insidious. He describes the appearances of the patient and the physical signs in advanced syringobulbia and adduces from a study of these the anatomical considerations devoted to the lower cranial nerves. There follows a review of the pontine cranial nerves and an interesting chapter on the autonomic abnormalities seen in syringobulbia. Up to date addenda follow every chapter, including illustrations of CT and MRI scans of the clefts. As a study of applied anatomy and pathological anatomy the book is a pleasure to read. The volume ends with clinical descriptions of hitherto unpublished cases.

Professor Ross, from the Section of Neurology, University of Manitoba, has accurately effected the translation, edited and annotated the work which certainly should be studied by any interested in the applied anatomy of the brainstem and those looking for a better understanding of the pathogenesis and clinical symptomatology of syringobulbia.

J. B. FOSTER

**The Rett Syndrome.** Edited by John M. Opitz, James F. Reynolds, La Velle M. Sparo and Hugo W. Moser. 1986. Pp. 432. New York: Alan R. Liss. Price £53.00

How was it possible, asks Hugo Moser, special editor of this volume, that it took until 1985 for American medicine to become aware for the first time of a disorder associated with mental retardation that equals phenylketonuria in frequency and severity? British and European paediatricians and child neurologists have been asking themselves the same question for some years, the scales having dropped from their eyes a little earlier. The first report by Andreas Rett in 1966 of a cerebral atrophic syndrome with hyperammonaemia in children caused a fluttering in the paediatric dovecotes, and a search for cases among the ranks of mentally retarded girls. Perhaps it was the suggested association of a biochemical abnormality, which proved to be unconfirmed, which caused so massive a perceptual defect; though noting the individual features in these girls, we did not recognize the very specific pattern which they composed. Only in 1983 did a European report of 35 cases of 'a progressive syndrome of autism, dementia, ataxia and loss of purposeful hand use in girls' appear, to be followed two years later by a series of 19 cases of Rett's syndrome in the west of Scotland. Thereafter, recognition dawned, the floodgates opened and most of those who deal with handicapped children have had the humbling but exciting experience of making the diagnosis both retrospectively in girls previously investigated for regression without result and in others presenting for the first time. So characteristic is the natural history of the disorder that the diagnosis comes quickly to mind when the history is related and, in the older patients at least, is usually confirmed on observation and examination.

The literature of the subject has naturally burgeoned, with many reports of individual cases or series from both clinical and investigative perspectives. Until recently the most useful publication has been in a volume of the Japanese journal *Brain and Development* reporting the proceedings of a Symposium on Rett's syndrome held in Vienna in 1984.

The present volume presents the proceedings of a workshop on Rett's syndrome held in Baltimore in November 1985. Those invited numbered 82, of whom more than half came from continental Europe, with 11 appropriately from Vienna, 5 from Japan and 2 from Britain—the authors of the Scottish paper.

Sixteen of the 40 contributions are on clinical aspects. These include 2 on the natural history, a series of 70 cases from Baltimore and of 23 from Glasgow. A suggested staging system is described by Hagberg and Witt-Engerström as applied to 29 Swedish patients aged 13–29 years. Rett's syndrome in an institution for the developmentally disabled is discussed by Adkins who describes 6 patients aged between 16 and 20 years; it seems certain that older women with the syndrome will be identified as knowledge increases; previously undiagnosed cases of well-known diseases such as tuberose sclerosis are often recognized for the first time in patients in long-stay hospitals for the mentally subnormal, and a 37-year-old woman initially investigated at the age of 5 years was recently diagnosed as having Rett's syndrome for the first time. Clinical papers of special interest are those of Olsson and Rett on shift to right-handedness in Rett's syndrome around the age of 7, and of Zappella on motivational conflicts. Breathing impairment is discussed by Cirignotta and colleagues. Gillberg addresses the question of the differential diagnosis from autism, which had been the initial diagnosis in between one and two-thirds of Swedish cases; this error has been very common and many 'autistic' girls no doubt remain to be reclassified; after the age of 2 the distinction becomes much clearer. The 3 papers on treatment include one on the ketogenic diet (improved seizure control resulted in the girls who tolerated it) and physical, occupational and music therapy are also discussed. Spinal deformity is common, though not universal, and its prevention is important, and must come to receive more attention.

Jellinger and Seitelberger contribute a paper on autopsy studies on 8 girls aged between 4 and 15 years, probably the largest series to date; the changes seen were not dramatic. Pterins, biotin and plasma endorphins are discussed. Further studies are needed to confirm or exclude their role, but preliminary data on plasma endorphins suggest a derangement of the dopaminergic system. Chromosome studies in three reports gave varied results, with the fragile site on X p22 being found in 6 of 10 Rett patients, 5 of the 9 mothers and 6 of the 12 control subjects in one series.

A case of ornithine transcarbamylase deficiency in a girl with many features of Rett's syndrome reported by Hyman and Batshaw is particularly interesting in view of the finding by Rett of raised ammonia levels in his original patients, a finding which was not confirmed in later cases. This case suggests that there may be other genetic disorders simulating Rett's syndrome.

The book closes with 4 stimulating contributions on genetics, an analysis of family and pedigree data, search for genetic markers, 'the consequences of a disorder where every case is a new mutation' and 'genetics and the future'.

Since all workers in the paediatric field are liable to encounter these hapless and pathetic girls and others caring for older handicapped patients many unknowingly harbour cases in their institutions, there is a need for education in the syndrome so that the diagnosis may be made early, the prognosis recognized and appropriate plans made for management. Many cases must still remain undiagnosed. The attaching of a diagnostic label to a handicapped child, though of little practical benefit, may be of great psychological value to her parents; they feel able to end their restless search for the 'cause' which they hope will lead to a cure, and to accept the child as she is and as she, sadly, will be. Parents can then benefit from contact with others to discuss their mutual problems. Parents' support groups are prominent in paediatric problems and have contributed greatly to care of the handicapped. It is significant that through the International Rett Syndrome Association the scientific workshop reported here was followed by a three-day meeting attended by 180 parents and 72 patients with a session at which many of the conference physicians examined each of the patients, an educational experience

of immense value. Studies similar to those reported here should certainly help towards better provision and management, and perhaps lead in time to more effective therapy.

This book deserves a wide readership.

E.M. BRETT

**Alcohol and Brain Development.** By J. R. West. 1986. Pp. 440. Oxford University Press. Price £45.00.

Concern over alcohol's potential to affect the developing fetus can be traced back to biblical times. In the story of Samson, the hero's mother cautioned 'Behold you are barren and have no children, but you shall conceive and bear a son. Therefore, beware, and drink no wine or strong drink. . . .' (*Judges*, 13:3-4). In spite of an awareness of such problems and particularly adverse effects on the developing brain, there has been little change recently in social attitudes to the use and abuse of this most commonly used 'drug'. Therefore *Alcohol and Brain Development* is a welcome addition to the growing field of literature which addresses these issues.

The editor, Dr James R. West, invited a wide-ranging group of authors to collaborate in the formulation of this book. Three basic sections deal with behavioural, neuromorphological and chemical aspects of alcohol's effects on brain development. Individual chapters in each section deal with both human and experimental models. In fact the book would be extremely valuable to any person interested in setting up experimental models of alcohol toxicity. Section three (Chemical aspects . . .) deals with a variety of molecular, hormonal and chemical changes in the brains of offspring exposed to alcohol during development. This is an interesting and informative section which draws together material which has not been reviewed in this style previously. The final chapter in this section (and the book) summarizes key issues raised by each of the authors and suggests directions for future research. Issues such as dose/time relationships during development, the questions of genetic susceptibility to alcohol toxicity, selective vulnerability of various brain regions and actual mechanisms of neurotoxicity have been addressed. Although complete answers to these issues are not yet available there is much information which could be used by scientific, social and clinical personnel working in this field.

Illustrations are of good quality and references are numerous and up to date. The book is well indexed. Although the book is heavily biased towards fetal effects of alcohol, there is much information which is equally relevant to effects of alcohol on mature brains and brain cells. In fact, although as the editor states, 'alcohol is the most commonly used neurobehavioural teratogen', the teratogenic effects and the direct toxic effects may be one and the same thing.

In summary, this book provides an excellent up-to-date review of the neurotoxicity of alcohol, particularly with regard to the development of the brain and would be a useful reference book for scientists and clinicians working in this field. Equally it has much material relevant to those working in the behavioural sciences. The final chapter is most useful in that the most relevant material from other authors in the book has been highlighted and organized into a conceptual framework.

CLIVE HARPER

**Blindsight: A Case Study and Implications.** By L. Weiskrantz. 1986. Pp. 187. Oxford Psychology Series No. 12. Oxford University Press. Price £19.15.

The importance of vision as a sensory modality in man is indicated by the fact that about half of all afferent inputs to the brain are visual. Studies of the effect on visual perception of lesions in the visual cortex in both nonhuman primates and man span a century and have always evoked controversy. Were the resulting scotomas absolute or not? Does some visual function return? If some visual function remains is this due to impaired function of recovering cortex or is it due to other subcortical visual pathways?

In the early 1970s it was generally considered that there was good evidence in nonhuman primates, in whom ablation was restricted to the striate cortices, that the resulting field defect was never absolute. In man, on the other hand, such lesions (of course more difficult to define anatomically) appeared to result in complete scotomas when assessed by conventional perimetry, although there were some cases in which recovery occurred leading to a relative defect.

It was at that time at the National Hospital for Nervous Diseases, London, that a patient, D. B., had an arteriovenous malformation removed from his occipital lobe involving much of the calcarine fissure. Shortly afterwards it was noted that he was able to locate objects in his blind field more skilfully than was expected, despite the fact that he denied any conscious awareness of their location. Thus the scene was set for a clinical investigation, performed over several years, by Professor Weiskrantz and his colleagues, of visual perception in D. B.'s blind visual field. An extensive analysis of the results of these investigations form the basis for this excellent monograph entitled *Blindsight*. This term was first introduced in 1974 by Professor Weiskrantz to describe D. B.'s visual performance and he defines it in the book as 'visual capacity in a field defect in the absence of acknowledged awareness'. The name for this phenomenon stuck and since that time many more patients have been described.

The book is divided into three parts. In Part 1 there is a review of the earlier studies describing the effect of occipital lesions on vision in primates. This leads on to the second part which forms the bulk of the book, in which the numerous experiments performed on D. B. are described in some detail. In modern clinical science the single case study is sometimes frowned upon. However, to read such a carefully planned series of investigations, their rationale and their shortcomings always explained, with comments rounding off each experiment is extremely illuminating. Much of the work in this book has not previously been published and it therefore provides an invaluable source record of probably the most extensive investigation of blindsight yet published. One particularly interesting part of this section of the book is that with each experiment there is a description of the patient's verbal commentary. Although in the definition of blindsight Professor Weiskrantz states '... in the absence of acknowledged awareness' subject D. B. sometimes had some awareness of the stimulus. In certain tasks D. B. considers his responses 'were all guess-work' or 'like tossing a coin', but at other times, for example, he 'feels something coming in'. When matching stimuli X vs O in the impaired and mirror-symmetrical normal field he states 'not much of an impression. I said 'O' when I got a slight bending wave—'X' when I got nothing at all ... I think I did a littler better than 50:50'. Despite this impression he only scored at the chance level. These verbal commentaries have rarely been quoted in previous studies of blindsight and as Professor Weiskrantz points out, they are of considerable interest.

In the final part there is a review of the literature concerning 'blindsight' followed by an appraisal of its status, associated issues and implications. This part of the book is again comprehensive and deals with all the experimental and theoretical problems which have bedevilled this field. Apart from scattered papers in the literature there has only been one previous large review of the subject in *Behaviour and Brain Science* (1983, 6, 423), and the opening discussion paper was anyway biased to the view that blindsight does not exist but is artefactual due to scattered stray light. It is, therefore, particularly useful to have Professor Weiskrantz's critical yet well balanced view of the problem of 'blindsight'. The monograph is extremely clearly written and will be of interest to all clinicians and neuroscientists interested in vision. As an exemplary example of the insights that can arise from the single case study it deserves a wider readership.

CHRISTOPHER KENNARD



**Language Processing in Children and Adults. An Introduction.** By M. Harris and M. Coltheart. 1986. Pp. 47. London: Routledge and Kegan Paul. Price £8.95 (paperback).

There are probably many neurologists, paediatricians and general practitioners, whose work brings them into contact with aphasic adults or children with abnormal language, who have become aware that significant changes have been occurring in the interpretation of such disorders, and that these changes owe something to psycholinguistic theories of language processing. The title of this easy-to-read book, which is written jointly by a developmental psychologist and a leading cognitive neuropsychologist, may well tempt them to look to it as a source of enlightenment.

Although the book is penetrating and authoritative in parts, its coverage of language processing is somewhat patchy, and the reader will find it much more concerned with models of language processing in adults than in children. In fact much of its coverage of children's language relates to the social settings in which language development takes place, rather than the mental processes which underlie the language behaviour of the child. For example, the account of a mother's nonverbal responses to a 7-month-old baby makes interesting anecdotal reading but is not related to a theoretical model. Under 'Later Development' we are told a good deal about children's strategies for understanding sentences (for example, the strategy of assuming that, if a sentence contains two nouns in subject and object position respectively, the animate noun will be the subject and the inanimate noun will be the object), but again we look in vain for something to relate these strategies to theories of mental processing which would give some coherence to these studies and prepare the reader for the section on developmental disorders of language.

Predictably, in view of the greater amount of work done by psycholinguists on the reading of single words than on other aspects of language processing, the book's strongest contribution to the discussion of the development of language and developmental disorders concerns reading. Four phases are proposed in learning to read in an alphabetical language like English: a sight vocabulary phase, at around 3 to 4 years, a discrimination-net phase at which the child selects from his vocabulary set on the basis of partial cues, a phonological recoding phase at about 8 years, by which stage children can pronounce nonwords and, finally, an orthographic phase where the visual spelling of words is established. Developmental dyslexia is discussed mainly in relationship to the last two of these four phases, since there is as yet virtually no evidence from dyslexic children to support the first two phases. Even interpretation of the last two phases relies heavily on studies of brain-damaged adults with reading disorders.

It is in the second half of the book, that relating to language in adults, that theories of language processing are more comprehensively propounded, although even here the approach is eclectic. Four models in particular are summarized: the logogen model of how single words are processed from input to output; the cohort model of the auditory comprehension of words (which claims that when we hear a word many other words which begin with the same sounds are aroused and are eliminated as more information is detected); the feature-detector model of how we read letters in a word; and a model of the microgenesis of sentences. For the first three of these models the detective story is told of how psycholinguist experimenters tested various hypotheses and counterhypotheses in laboratory settings; the last model is sketchily presented without any of the supporting evidence from the study of speech errors on which it was based. The section on the processing of discourse is also limited, in that discourse appears to be restricted to narrative in experimental tasks.

The book's final chapter, on acquired disorders of language, brings into focus the strengths and the limitations of the current psycholinguistic approach to the aphasia. It includes a diagram of 'an information processing model of language' which demonstrates how we read aloud (i.e., go from print to speech) or write to dictation (i.e., go from speech to print). The model is incomplete (for example, it implies that to repeat speech we need to understand it, which the existence of transcortical aphasia clearly demonstrate is not the case) and it is couched only in terms of single words. Nevertheless the model has been influential in distinguishing types of acquired dyslexia and dysgraphia according to which of the routes from print to speech or vice versa are dysfunctioning. Harris and

Coltheart argue for the use of such theoretically based models in defining syndromes, and point out the disadvantages of the 'clinical' use of syndromes which group together diverse symptoms. It is a pity that they did not apply at least the principles they used in discussing the acquired dyslexias to their analysis of aphasia, for which they even perpetuate the anachronistic terms of expressive and receptive aphasia. They give a cursory account of the classical syndromes of Broca's, Wernicke's, conduction, anomic, transcortical and global aphasias, but draw attention to the need for a theoretical account for only one of these.

Aside from some inaccuracies and oversimplifications (e.g., that 'hit' as a verb has three obligatory arguments, and that phonological errors are 'errors of pronunciation') there is much to enjoy in the book. In a field where the temptation to resort to jargon is strong, its style is clear and technical terms are explained and illustrated. For example, the description of Chinese orthographic characters is vividly illustrated by the list of ladies available at the Metro ballroom in Singapore, 'all beautiful ladies for your choice', whose names are arranged in alphabetical order according to the number of strokes they contain.

In summary, the book only partly achieves its aim of being an introduction to language processing in children and adults, but for those readers who are unfamiliar with the psycholinguistic literature and its relevance to language pathologies, a selective sampling of sections of the book will give them an inkling about the potential of this approach for the better understanding of language disorders.

RUTH LESSER

**Handbook of Clinical Neuropsychology, Volume 2.** Edited by Susan B. Filskov and Thomas J. Boll. 1986. Pp. 716. Chichester: John Wiley. Price £46.05.

A primary objective of the *Handbook of Clinical Neuropsychology*, Volume 2, edited by Susan B. Filskov and Thomas J. Boll, is to serve as a reference that supplements, but does not recapitulate, the material available in Volume 1 of the Handbook. The goal is to cover a broad range of topics with special emphasis on issues that are likely to be salient during the next half decade. The book is clearly targeted for the psychologist, particularly the clinical neuropsychologist, and students of psychology; appeal to the neurologist and neuroscientist will be more limited.

The book is quite varied. From the cast of contributors, to the topics included, to the quality of the material, there is great diversity. This at once enhances and detracts from the overall quality of the volume. One finds a wide array of reference material not present elsewhere under a single roof; unfortunately, several of the dwellers belong either in another volume, or in an era past, and the book could be half its current size and lose little useful information. On balance, though, there is considered treatment of a number of important topics not covered in previous works of this sort, and the Handbook deserves a place on the reference shelf of the clinical neuropsychologist.

The Handbook is divided in four parts, the first of which includes two chapters describing the relationship between neuropsychology and its first cousins—behavioural neurology and health psychology. The veteran neuropsychologist will find little new information here although the student of the field may benefit from the broad perspective that is provided. The goal of delimiting the field of neuropsychology with respect to its counterparts in medicine and psychology is worthwhile, although this is accomplished more completely in several of the final chapters of the Handbook.

Part Two, composed of Chapters 3 to 9, deals with assessment, traditionally the stronghold of neuropsychology. This area is well covered in a number of extant volumes, but the Handbook nonetheless manages to provide relevant and nonredundant information. Chapter 3, for example, provides an excellent analysis of the psychometric foundations of assessing behavioural and cognitive effects of brain injury. The descriptions of neurological diagnostic tests presented in Chapter 4 are relevant and refreshingly easy to follow. Chapters 5 and 6, timely pieces on the neuropsychological assessment of adults and children, also deserve their places in the Handbook. For the clinician who

specializes in assessment of adults but who nonetheless encounters an occasional child patient, the information available in Chapter 6 may be especially useful. It introduces the reader immediately to the major instruments and issues involved in the neuropsychological evaluation of children. The material in Chapter 7, concerning the assessment of aphasia, is available in nearly all recent volumes on neuropsychology. Chapter 8 provides a cursory treatment of the demographic variables of sex and handedness. A number of important issues are raised in Chapter 9, which deals with the relationships of disease process, onset and course, to neuropsychological test performance. There are disappointingly few specific conclusions but the questions addressed in this chapter are deserving of the attention of neuropsychologists.

Part Three of the Handbook encompasses a number of specific disorders, including medical conditions, personality and affective disturbances, and sleep disorders. Comprised of Chapters 10 to 16, this section provides a very useful collection of issues and conditions that are likely to constitute a major portion of the casework of a neuropsychologist. This is the strongest section of the Handbook and the most useful addition to Volume 1. Chapter 10 provides original information on the neuropsychological consequences of a variety of medical conditions whose impact on cognition and behaviour is secondary but probably underestimated. Chapter 11 presents a timely and cogent argument for the importance of knowledge of psychopathology in a well-rounded understanding of the behavioural effects of brain damage. A rather uncritical treatment of affective disturbances associated with brain damage is provided in Chapter 12. Chapters 13 and 14, which deal with the psychological and neuropsychological correlates of the two common neurological diseases, epilepsy and multiple sclerosis, are valuable references for the practising neuropsychologist. Chapter 15, on dementia, and Chapter 16, on sleep disorders, are also important contributions. The latter, which is described by the editors as the first formal treatment of the topic of sleep disorders in the neuropsychological literature, is extensive, and should be valuable to academic and clinical neuropsychologists.

Part Four of the Handbook is a hotchpotch of chapters dealing with issues such as rehabilitation, computerized assessment, statistics, localization of function, and training. The appeal of Chapter 20, a technical and theoretical discussion of issues of localization in the primate forebrain, will be minimal for the typical reader of this Handbook. Chapters 17 and 19, dealing with rehabilitation and statistical models, respectively, are indispensable and unique additions to the rest of the Handbook; this material is much too frequently eschewed by textbooks on neuropsychology. A brief discussion of the application of computer technology to the interpretation of neuropsychological test data constitutes Chapter 18. The book closes with Chapter 21, which presents an astute summary of the issues involved in the graduate and postgraduate training of clinical neuropsychologists.

On balance, this second volume of the Handbook will supplement nicely the material presented in Volume 1. Although the average quality of the chapters might have been higher, the book represents a current and valuable reference volume for the clinical neuropsychologist. Filskov and Boll are to be congratulated on their timely promotion of the field of neuropsychology as both profession and science.

DANIEL TRANEL

**Recent Advances in Neuropathology 3.** Edited by J. B. Cavanagh. 1986. Pp. 167. Edinburgh: Churchill Livingstone. Price £30.00.

This is the third volume of *Recent Advances in Neuropathology* to provide up-to-date and critical reviews on issues of current importance in the rapidly expanding field of neuropathology. It is thinner in format than the preceding volumes from 1979 and 1982 and contains 7 chapters. The first is an excellent review on new perspectives on glial cells by Mirsky and Jessen. In the section on intermediate filaments they conclude that the glial fibrillary acidic protein exhibits antigenic heterogeneity and is

not restricted to astrocytes but shows a widespread and complex distribution among central and peripheral glia. Among the cell surface macromolecules, galactocerebroside is expressed also on nonmyelin-forming Schwann cells, suggesting that the glycolipid is not only a component in myelin sheaths but may also be involved in axonal-glial interactions. The interaction between the basal lamina and growing axons is beginning to be understood in molecular terms with the key molecules laminin and fibronectin promoting the elongation of PNS neurites. The evidence that the macroglial cells of the rat optic nerves consist of two types: type 1 astrocytes which arise early in development and type 2 astrocytes and oligodendrocytes which differentiate from a common progenitor cell, is also reviewed.

Coakham and Brownell have critically reviewed the usefulness of monoclonal antibodies in the diagnosis of cerebral tumours and cerebrospinal fluid neoplasia. The panel of antibodies presently used for tumour diagnosis in Bristol is given, with examples of how they can significantly contribute to a correct diagnosis in quite a number of cases. They are particularly helpful in distinguishing lymphomas from other small round cell tumours in the brain. This is a rapidly expanding field and new generations of antibodies will soon appear, including such that may recognize the presence of oncogene products in tissue sections.

Dyck and coworkers illustrate how their imaging system for nerve morphometry can be used to elucidate the underlying mechanisms of diabetic polyneuropathy. The arguments for a vascular versus metabolic cause of diabetic polyneuropathy are reviewed and by using their criteria for ischaemic nerve injury, that is, sufficient vessel alteration and characteristic nerve fibre pathology with central fascicular or sector fibre loss beginning at proximal levels and a mixture of axonal degeneration and segmented demyelination, they reach the conclusion that the lesions are compatible with an ischaemic neuropathy. The other chapters in the book review host resistance to gliomas (Bullard and Bigner), ultrastructural classification of pituitary tumours (Howath and Kovacs), neuropathies in domestic animals (Griffiths and Duncan) and the neuropathology of decompression sickness (Palmer).

To quote the editor J. B. Cavanagh, this book shows how the active field of neurobiology inspires neuropathological research to understand the expression of diseases and disturbances in the nervous system. This is strongly emphasized by the first chapter on glial cells which in itself makes this volume worth acquiring.

KRISTER KRISTENSSON

**Comparative Neurobiology of the Basal Ganglia.** By Andre Parent. 1986. Pp. 335. Chichester: John Wiley. Price £57.50.

The anatomy, physiology, pharmacology, neurochemistry and clinical significance of the basal ganglia together constitute a major contemporary research front, and one which is undergoing rapid advance. Dr Parent's book is, therefore, particularly timely. In it he summarizes and synthesizes from the wealth of data which have become available over recent years, paying particular attention to neuroanatomical findings that have been made with modern tracing techniques.

An important feature of the book is that it brings together data on both mammalian and nonmammalian species. Almost the first half of the book deals with nonmammals. Major section headings in this part of the book are: Basal Ganglia and Vertebrate Phylogeny, Telencephalic Organization in Fishes, Telencephalic Organization in Amphibians, Basal Ganglia in Reptiles, Basal Ganglia in Birds. The rest of the volume is devoted to the mammalian basal ganglia in sections entitled: Basal Ganglia in Mammals: An Overview, Mammalian Striatum: A Highly Heterogeneous Structure, Mammalian Pallidum: A Source of Redundancy, Mammalian Substantia Nigra: A Dual Structure, Basal Ganglia versus Limbic Structures.

The breadth and depth of the material covered are considerable achievements in themselves. The text is highly readable, concise and firmly authoritative. The style of the text clearly reflects the

author's enthusiasm for, and command of, his subject matter. The book is to be highly recommended to all serious students of the basal ganglia.

A. R. CROSSMAN

**Basic Mechanisms of the Epilepsies.** Advances in Neurology, Volume 44. Edited by A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury and R. J. Porter, 1986. Pp. 1120. New York: Raven Press. Price \$108.50.

**Kindling 3.** Edited by J. A. Wada. 1986. Pp. 576. New York: Raven Press. Price \$81.50.

**Neurotransmitters, Seizures and Epilepsy III.** Edited by G. Nistico, P. L. Morselli, K. G. Lloyd, R. G. Fariello and J. Engel. 1986. Pp. 525. New York: Raven Press. Price \$78.00.

Raven Press appears to be trying to corner the market for books on epilepsy. The three books reviewed here were all published by them within a few months, all are multiauthor works based on scientific meetings, and all address the fundamental mechanisms of the epilepsies and their experimental models. In this review I will briefly consider each in turn, before attempting to draw more general conclusions.

*Basic Mechanisms of the Epilepsies* is the most ambitious of the three works. It is a welcome, worthy and somewhat overdue successor to Jasper, Ward and Pope's original book of the same title published in 1969. In common with its illustrious predecessor it verges on the encyclopaedic (within the constraint of its trendy subtitle 'Molecular and Cellular Approaches'). It contains sections on: biochemical genetics; intracellular mechanisms; intercellular mechanisms; spread and arrest of seizures; cellular damage; and mechanisms of epilepsies in man. The preface carries the disclaimer, also found in the 1969 volume, to the effect that limitations of space prevent the work from being all-inclusive. It seems to me to be sufficiently inclusive; either more topics or more detail in the existing chapters would make the whole unmanageable. Although a few read like papers in primary journals, the majority of the 53 chapters represent real attempts by their authors (prompted by the editors) to review, to comment and to speculate on their respective fields. Some of them actually are a pleasure to read! I certainly gained the impression that all those involved have made a major effort: the authors, the editors, the publishers and the organizers of the two conferences on which the book has been based. The book is well produced, properly typeset and with decent reproduction of its figures. The index is extensive and comprehensive (although I am not familiar with the convention that places 'sympathetic ganglion' to 'synchrony' between 'steroids' and 'substance P'; a minor, but surprising error in view of the quality of the book as a whole). Overall, I believe that *Basic Mechanisms of the Epilepsies* will be an important source for many years to come. If you or your librarian are only prepared to buy one book on epilepsy this year, this should be it.

*Kindling 3* concentrates on a single experimental model of epilepsy. The term 'kindling' was coined by Graham Goddard, whose most untimely death occurred earlier this year. Kindling is the progressive, permanent reduction in seizure threshold that occurs when certain brain regions are stimulated repeatedly every few hours to days. The 28 papers in this volume are more concerned with new results than with providing an overview, not unreasonably, as this book is aimed at a much more specialist audience than *Basic Mechanisms of the Epilepsies*. There appears to have been a (welcome in my view) shift away from the search for mechanisms based on single specific transmitter systems towards considerations of neuronal circuitry, both for the establishment of the kindled focus, and for the propagation and generalization of seizures. Unfortunately, the quality of production of this book leaves much to be desired. It suffers from some of the worst features of camera-ready copy: a variety of typefaces and pitches, some of which I found impossible to read for any length of time, and poor reproduction of figures (particularly deoxyglucose autoradiographs). However, it does have major redeeming features. It has a reasonable subject index, and, interestingly, a classified bibliography of papers published on kindling from 1980-1985, presumably compiled by Wada.

Perhaps the biggest asset of *Kindling* is that it represents a real common interest to the participants. This comes across in the verbatim (and apparently unedited) transcripts of the discussions, which add significantly to the book. My final impression from this book is that kindling remains as enigmatic as ever, but, even if we never succeed in fully understanding its mechanisms, it certainly has been an immense stimulus to research on the epilepsies.

*Neurotransmitters, Seizures and Epilepsy III* seems much less cohesive than *Kindling*, perhaps because it stems from a bigger meeting, or perhaps because it centres on something that is more difficult to define: an approach, or level of analysis rather than a specific model. The final discussion revealed that the participants themselves disagreed on the goals of the meeting: on whether the emphasis on neurotransmitters had become too diluted, on whether the papers had sufficient clinical relevance, and on the merits of different kinds of experimental strategy. Perhaps this explains why the discussions of individual papers were generally much shorter than those in *Kindling*. One point that surprised me was how little overlap existed in the contents of these two books, and indeed in the participants at the two meetings. Can we gain any overview from the 36 chapters in this book? Perhaps two-thirds are to some extent concerned with amino acids as transmitters, and the majority of those primarily are about inhibition and/or GABAergic synapses or receptors. The idea that inhibition is an important factor in epilepsy is hardly new, but what may be is a shift away from thinking simply in terms of a loss of inhibition towards speculation on inhibitory circuits causing abnormal degrees of synchronization (it should not be forgotten that such mechanisms were proposed for cortical synchronization during alpha rhythm and barbiturate spindles at least 25 years ago). Other topics that appear to be developing in popularity are the glutamate receptor subtype selective for N-methyl-aspartate, and the role of intracellular calcium in neuronal discharges and in long-term modulation of neuronal properties. Again the publishers have used camera-ready copy, but here the papers are in uniform typeface, and are all justified to both sides of the page. This must have involved the editors or publishers in significant retyping, but the end product is more attractive as a result.

*Kindling* and *Neurotransmitters, Seizures and Epilepsy* both are the third in their respective series of meetings, which seem to occur every few years. By allowing the selected participants a reasonable number of pages (averaging 17 and 13, respectively) they certainly do add up to more than simply books of meeting abstracts; they give a useful overview of the state of play in their respective fields, within the constraints of the participants able and willing to attend. However, such books will have a useful lifespan of no more than a few years, which means that rapid publication is important. Raven Press managed 14 months and 11 months, respectively. If proper typesetting would have delayed publication further, perhaps the use of camera-ready copy is justified. If so, I would strongly urge publishers to standardize on a decent typeface, as used for *Neurotransmitters, Seizures and Epilepsy*, and not for *Kindling* 3. The use of camera-ready copy has not made these books particularly cheap, but they must both suffer from limited specialist markets. On the other hand, *Basic Mechanisms of the Epilepsies* clearly required a much greater degree of organization and editorial control, and much more effort by its authors. Therefore it is no surprise to find a much longer delay to publication from the two meetings on which it was based ( $2\frac{1}{2}$  to  $3\frac{1}{2}$  years). I am convinced that it will have a longer useful lifespan than the other two works, but given the ever accelerating pace of research in their basic mechanisms of the epilepsies, I hope that we will not need to wait 17 years for its next update.

JOHN G. R. JEFFREYS

## ANNOUNCEMENTS

### European Neurological Society

The European Neurological Society (ENS) has been founded to foster cooperation between neurologists and those working in related disciplines within Europe. Meetings will be held biennially. The participation of individuals from other areas of the world is welcomed. The biennial meetings will provide instructional courses

for neurologists in training, up-date symposia, and sessions for the presentation of original work, either as platform or poster presentations. The first meeting will be held in Nice from June 19-21, 1988, when the teaching programme will include courses on peripheral neuropathy, neuroimaging, ageing and dementia, and neurovirology/neuroimmunology. There will be symposia on physiological and pathological aspects of cerebral blood flow, clinical neuropharmacology, and neurogenetics.

Active membership of the ENS will be by election from clinicians and scientists whose chief interest is directed towards practice, teaching or research in neurology and cognate fields. Active membership will become effective only after contribution to a meeting of the ENS. Junior members may be elected from members engaged in postgraduate studies in neurology or related disciplines.

Further information about the ENS may be obtained from the Secretary, Prof. G. Said, Service de Neurologie, Hôpital de Bicêtre, 94287 Le Kremlin Bicêtre Cedex, France.

#### **American Association of Electromyography and Electrodiagnosis**

The 34th Annual Meeting of the AAEE will be held in San Antonio, Texas, on October 16-17, 1987. This will be preceded, on October 14-15, by the AAEE 10th Annual Continuing Education Courses. Further information may be obtained from Ella M. Van Laningham, Executive Director, 732 Marquette Bank Building, Rochester, MN 55904, USA (tel. 507/288-0100).

## *Travel Grants For Young Neuroscientists*

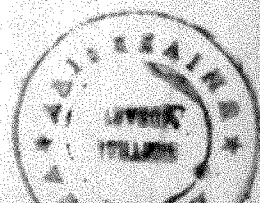
The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
  - (a) an abbreviated curriculum vitae and a list of any relevant publications;
  - (b) statement of age and post currently held;
  - (c) a concise account of the purpose of the proposed visit;
  - (d) a recommendation from the head of department (where appropriate);
  - (e) a letter of acceptance from the department to be visited;
  - (f) a statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always be taken of reduced air fares when available.
2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.
3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to

Dr D. A. S. Compston,  
Department of Neurology,  
University Hospital of Wales,  
Heath Park,  
Cardiff CF4 4XW, UK







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## SERVICE TO NEUROSCIENCE

# THE PATTERN OF NEUROPSYCHOLOGICAL IMPAIRMENT ASSOCIATED WITH LEFT POSTERIOR CEREBRAL ARTERY INFARCTS

by E. DE RENZI, A. ZAMBOLIN *and* G. CRISI

*(From the Departments of Neurology and Radiology, University of Modena, Italy)*

## SUMMARY

We investigated the neuropsychological correlates of left posterior cerebral artery (LPCA) infarcts with a quantitative systematic approach and found a pattern of impairment extending well beyond the classical syndrome of alexia without agraphia. Sixteen consecutive patients with CT scan evidence of an infarct confined to the territory of LPCA were given a battery of tests assessing the following abilities. (1) Reading and writing; (2) naming and pointing to colours; (3) naming the same 30 objects on visual (objects and coloured photographs), tactile and verbal presentation; and (4) verbal memory. These tests were administered to large control samples and the performance of LPCA patients was considered pathological if it fell below the score of the last or second to last control patient.

Seventy five per cent of PCA patients had alexia without agraphia. Although a lesion of the CT scan slice where the pineal is represented appeared to be crucially associated with alexia, the severity of the disorder increased when contiguous upper or lower slices were also involved. Not only colour anomia, but also object and especially photograph anomia could almost always be shown in alexics and were highly correlated with the degree of the reading impairment. The naming deficit was also present when items were presented in the tactile and verbal modality, in spite of the integrity of the oral language areas. Every right-handed patient, alexic as well as nonalexics, was impaired on at least two of the three verbal memory tests and most on all of them. The findings are discussed in terms of the anatomofunctional mechanisms subserving verbal memory and the transmission of visual information to the speech areas.

## INTRODUCTION

Infarcts in the cortical territory of the posterior cerebral artery (PCA) of either side are usually associated with contralateral homonymous hemianopia as a consequence of the damage to optic pathways or calcarine cortex. When the lesion is in the left hemisphere, the clinical picture is enriched by a spectrum of cognitive disorders, ranging from alexia without agraphia to colour anomia, object agnosia and verbal amnesia. The last symptom stands apart and reflects the involvement of the medial temporal cortex, while the first three have a common anatomical and functional basis, in that they point to occipital damage and imply a defective

performance in the visual sphere. This does not mean that they necessarily occur together or with equal frequency; in fact alexia without agraphia and, to a lesser degree, colour anomia are said often to be associated with left PCA infarcts, while object agnosia would be exceedingly rare, to the point that for some authorities it only follows bilateral occipital damage (Alexander and Albert, 1983). The reason of this dissociation is not altogether clear.

Alexia without agraphia and colour anomia are currently interpreted as the result of the interruption, at the level of the splenium or of the left occipitoparietal white matter, of the pathways linking the right occipital lobe, which alone receives the visual stimuli, with the speech area of the left hemisphere, which alone can encode them verbally or decode them (Dejerine, 1892; Geschwind, 1965). Why the same interruption of interhemispheric communication does not apply to other types of visual stimuli, causing visual agnosia (or, to be more precise, optic aphasia) in addition to the inability to name letters and colours, remains a matter of debate. Faced with this question, Geschwind (1965) resorted to the hypothesis that objects, being experienced through multiple modalities, can exploit alternative pathways to circumvent the block of visual information. For instance, the right occipital area may transmit what it receives to the right parietal lobe and arouse the somesthetic engrams of objects stored therein, which in turn can easily reach the speech area, crossing the corpus callosum anterior to the lesion. The same route is precluded for letters and colours which are only experienced visually. A problem with this interpretation is that letters and colours are not the only instances of stimuli which we know uniquely through vision. There are many other things that we never experience with senses other than visual, for example, whatever exists in the sky (the sun, the moon, the stars, the clouds), trees, mountains, lakes, buildings, monuments, etc.

The issue is further complicated by the small but not negligible number of cases of visual agnosia and optic aphasia reported following splenial and left occipital damage (Freund, 1889; Lissauer, 1890; Müller, 1892; Souques, 1907; Niessl von Mayendorf, 1935; Scheller, 1966; Lhermitte *et al.*, 1973; Caplan and Hedley-White, 1974; Hécaen *et al.*, 1974; Pillon *et al.*, 1981; Morin *et al.*, 1984; Ferro and Santos, 1984; Larrabee *et al.*, 1985), which are difficult to reconcile with the thesis that objects can easily bypass the interruption of interhemispheric visual pathways. Do they simply represent an exception to the rule, or do they magnify a deficit that in a less conspicuous form is also present in other cases? A perusal of the recent literature on pure alexia enabled Michel *et al.* (1979) to point out that errors in naming objects were mentioned in more than half of the reported cases (26 out of 46), an incidence not substantially less than that (30 out of 46) found for colour anomia. Although unexpected, this proportion may be an underestimate, as in some cases no data are provided and in others only a cursory examination at the bedside was performed.

The visuoverbal disconnection theory implies that the deficit is modality specific and that the same stimuli which cannot be named on visual confrontation are

named in response to verbal questions or when they are presented in the tactile modality. These are indeed the criteria traditionally required to make the diagnosis of visual agnosia or optic aphasia. Yet the literature (reviewed by Morin *et al.*, 1984) reports cases where naming difficulties involved both the visual and the tactile modalities, in the absence of sensory deficits and aphasia, and Critchley (1964) surmised that this may be the rule rather than the exception.

Summing up, the clinical pattern associated with left PCA infarcts appears to be more entangled than the traditional picture, emphasizing alexia and colour anomia only, would imply. We do not even know whether these symptoms are invariable concomitants of left PCA infarcts or, if negative cases can occur, possibly related to the location and size of lesion. A prospective study, systematically assessing the whole array of disabilities mentioned in the literature, can possibly improve our understanding of the subject. The present investigation reports the scores obtained by 16 consecutive patients with left PCA infarction on a battery of tests tapping the following performances: (1) reading; (2) writing; (3) naming and pointing to colours; (4) naming objects on verbal, tactile and visual confrontation, the last performance tested with both objects and their photographic representation; and (4) verbal memory.

## MATERIALS AND METHODS

### *Patients*

All patients admitted to our department in the years 1983–1985 and presenting with an infarct in the territory of the left PCA artery, documented by CT scan, were investigated. There were 16 cases and their biographical and clinical data are summarized by Table 1, together with the time post-onset at which testing was carried out. All patients underwent neurological examination and visual field confrontation testing, supplemented in most of the cases by Goldman perimetry. Colour vision in the residual field was not tested.

TABLE 1. CLINICAL DATA OF PCA PATIENTS

| <i>Case</i> | <i>Sex</i> | <i>Age (yrs)</i> | <i>Yrs of schooling</i> | <i>Duration of infarct</i> | <i>Visual field defects</i>     |
|-------------|------------|------------------|-------------------------|----------------------------|---------------------------------|
| 1           | M          | 73               | 5                       | 7–12 days                  | Hemianopia                      |
| 2           | M          | 75               | 4                       | 45 days                    | Hemianopia                      |
| 3           | M          | 65               | 5                       | 6 months                   | Upper quadrantanopia            |
| 4           | F          | 28               | 13                      | 15 days                    | Upper quadrantanopia            |
| 5           | M          | 62               | 7                       | 8 days                     | Hemianopia                      |
| 6           | M          | 62               | 5                       | 3 months                   | Hemianopia with macular sparing |
| 7           | M          | 75               | 3                       | 1 year                     | Hemianopia                      |
| 8           | M          | 66               | 5                       | 50 days                    | Hemianopia                      |
| 9           | F          | 56               | 8                       | 20 days                    | Hemianopia                      |
| 10          | M          | 69               | 3                       | 15 days                    | Upper quadrantanopia            |
| 11          | M          | 76               | 2                       | 20 days                    | Hemianopia                      |
| 12          | F          | 68               | 5                       | 10 days                    | Hemianopia                      |
| 13          | M          | 59               | 5                       | 8–17 days                  | Hemianopia                      |
| 14          | M          | 78               | 8                       | 20 days                    | Upper quadrantanopia            |
| 15          | M          | 74               | 3                       | 20 days                    | Hemianopia                      |
| 16          | M          | 62               | 5                       | 75 days                    | Hemianopia                      |

### Tests

*Reading.* The patient was required to read out 21 letters and 12 words (from 4 to 11 letters). Reading comprehension was tested with 20 written words, each to be matched with the corresponding picture on a four-choice display and with 14 items of a written version of the Token Test. In all these tests one point was given for each successful item, ignoring self-corrected errors.

*Writing.* Ten words were written to dictation. Each word was credited 1 point if the performance was flawless, 0.5 if a single letter was substituted, added, or omitted and 0 for any other type of error.

*Colour.* A set of 10 coloured chips was presented for the patient first to name them and then to point to them on verbal confrontation.

*Object naming.* The patient was requested to name 30 common objects in the following four conditions. (1) Visual presentation, objects. Each item was presented in full view, the patient being prevented from handling it. (2) Visual presentation, photographs. A set of coloured photographs of the same objects was shown. (3) Tactile presentation, objects. The blindfolded patient was handed the object and required to palpate it with both hands. (4) Verbal presentation. Naming was requested in response to a definition of the object, always based on its use, for example what do you use to drive a nail into a wall? The time limit was 30 s for each condition. A correct answer given in 10 s was scored 2, in 11–30 s, 1. Thus the maximum score was 60. Conditions 2 and 4 were tested in one session and conditions 3 and 1 in another session, 24 h apart.

*Verbal memory* was assessed with the following tests. (1) Learning to criterion (two successful repetitions) a 10-word list up to a maximum of 20 trials. The score was the ratio between the total number of words recalled and the number of trials to criterion (20, if the criterion was not reached). Maximum score: 10. (2) Learning 10 paired-associates (5 easy and 5 difficult): three trials. One point was given for a difficult association correctly recalled and 0.5 for an easy one. Maximum score: 22.5. (3) Story recall, immediate and after a 10 min interval. The story had 26 scorable bits of information and each correctly recalled bit was scored 1 point. Maximum score: 52.

### Criteria used to identify defective patients

To identify patients who failed on a given test, we compared their performance with that of controls who were given the same test in the present or a previous investigation. The numbers investigated were 130 for the reading and writing tests (unpublished data), 100 for the colour tests (De Renzi and Spinnler, 1967), 70 for the naming tests (current investigation) and 100 for the verbal memory tests (De Renzi *et al.*, 1977). For any test, except the verbal memory tests, a PCA patient's performance was considered pathologically impaired if it fell below the poorest score found in the corresponding control group (cut-off score). By computing the one-side distribution-free beta content tolerance limit (Guenther, 1972), it is possible to estimate the percentage of the normal population that can be expected to score below the cut-off score and the type one error probability associated with this statement, both values being dependent on the size of the control sample. With our samples these values are as follows: reading and writing tests: 2% ( $P < 0.05$ ), colour tests: 3% ( $P < 0.05$ ), naming tests: 4% ( $P < 0.05$ ).

For the verbal memory tests, the identification of impaired patients was based on the findings of a previous study (De Renzi *et al.*, 1977), in which the scores of 100 controls and 20 amnesic patients were submitted to discriminant analysis. This yielded for each test a criterion value, discriminating at best a normal from a pathological performance.

## RESULTS

### Reading and writing

The PCA patients' performance on the reading tests and writing to dictation is shown in Table 2, together with the cut-off scores. Three patients (Cases 12–14)

TABLE 2. READING AND WRITING SCORES

|                                                    | <i>Patients</i> |     |   |     |     |     |     |   |     |     |    |    |     |     |    |    |
|----------------------------------------------------|-----------------|-----|---|-----|-----|-----|-----|---|-----|-----|----|----|-----|-----|----|----|
|                                                    | 1               | 2   | 3 | 4   | 5   | 6   | 7   | 8 | 9   | 10  | 11 | 12 | 13  | 14  | 15 | 16 |
| Letters<br>(cut-off score:<br>21)                  | —               | 11  | 5 | 21  | 11  | 18  | —   | 9 | 17  | 20  | 7  | 21 | 21  | 21  | 21 | 21 |
| Words<br>(cut-off score:<br>12)                    | 4               | 0   | 0 | 10  | 0   | 5   | 4   | 0 | 0   | 9   | 0  | 12 | 11  | 12  | 6  | 12 |
| Word com-<br>prehension<br>(cut-off score:<br>18)  | 12              | 0   | 0 | 17  | 0   | 3   | 1   | 0 | 0   | 13  | 0  | 17 | 18  | 20  | 10 | 15 |
| Sentence<br>comprehension<br>(cut-off<br>score: 9) | —               | 0   | 0 | 8   | 0   | —   | —   | 0 | 0   | 6   | 0  | 9  | 8   | 8   | 3  | 6  |
| Writing to<br>dictation (cut-<br>off score: 6.5)   | 10              | 8.5 | — | 9.5 | 6.5 | 7.5 | 5.5 | 7 | 9.5 | 6.5 | 6  | 9  | 6.5 | 7.5 | —  | 8  |

— = test not given.

did not complain of alexia and performed in the normal range on practically every test. One of them (Case 14) was left-handed. Case 4 read laboriously through self-corrected errors, but attained nearly normal scores. Cases 10 and 16 were mildly impaired on reading words and sentences. All other patients were markedly impaired, most of them at the level of reading out single letters and 6 scored 0 on the word tests. The error pattern was typical for pure alexia (Henderson *et al.*, 1985): increasing difficulty with longer words, visual paralexias, 'conduites d'approche'.

Case 2 refused to write to dictation, while the relatives of Case 15 reported that he had always been unable to write, due to his low educational level (three years of schooling), although he had learnt to read. The patients that could be tested performed strikingly better on writing than reading and only 2 (Cases 6 and 11) scored marginally below the cut-off point.

### *Colour verbal identification*

The patients' scores on the two verbal colour tests are shown in Table 3, which also presents the cut-off points found in 100 normal controls (De Renzi and Spinnler, 1967).

Two patients were not tested. Three nonalexia patients (Cases 4, 12 and 14) and 1 mildly alexia patient (Case 16) performed in the normal range. The fourth nonalexia patient (Case 13) and the second patient with mild alexia (Case 10) showed a marginal decrement on colour naming, but not on pointing to colours. The remainder were severely impaired.

TABLE 3. VERBAL IDENTIFICATION SCORES FOR COLOUR

|                        | <i>Patients</i> |          |          |          |          |          |          |          |          |           |           |           |           |           |           |           | <i>Cut-off<br/>score</i> |
|------------------------|-----------------|----------|----------|----------|----------|----------|----------|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|--------------------------|
|                        | <i>1</i>        | <i>2</i> | <i>3</i> | <i>4</i> | <i>5</i> | <i>6</i> | <i>7</i> | <i>8</i> | <i>9</i> | <i>10</i> | <i>11</i> | <i>12</i> | <i>13</i> | <i>14</i> | <i>15</i> | <i>16</i> |                          |
| Colour naming          | 4               | 3        | 3        | 10       | 2        | —        | —        | 4        | 5        | 7         | 4         | 10        | 7         | 9         | 5         | 9         | 8                        |
| Pointing to<br>colours | 5               | 7        | 3        | 9        | 7        | —        | —        | 8        | 7.5      | 9         | 5.5       | 10        | 9         | 10        | 6         | 10        | 8                        |

— = test not given.

*Object naming*

Table 4 reports the scores obtained by PCA patients in the four naming conditions and the cut-off points. In the tactile test the poorest control subject was an outlier, with a score 10 points inferior to that of the penultimate subject; the scores of the next to the last normal control subject are also reported. Nine patients fell below the cut-off point on naming objects, 10 on naming photographs, 3 on tactile naming and 8 on naming to description. There was 1 additional patient who fell below the score of the penultimate control subject on the photograph test, 1 on the object test, 2 on the verbal test, and 7 on the tactile test.

With the exception of Case 6, every patient who was dyslexic was impaired in naming photographs, and the same patients, except the two mild dyslexics (Cases 10 and 16), were also impaired in naming objects. The 4 nonalexics scored in the normal range on the entire battery, save Case 4 who failed on verbal naming.

Although the number of PCA patients with a pathological score is approximately the same in the object, photograph and verbal test, Table 4 suggests that photograph scores depart more from the cut-off point than other scores. To verify this impression we computed in control subjects the difference between the scores of every pair of tests and took the highest values in either direction as the cut-off points of the difference. For instance, the difference between object naming and verbal naming ranged in normals from 6 to  $-4$ . PCA patients whose difference was higher than 6 were considered pathologically impaired on the verbal test in

TABLE 4. NAMING TEST SCORES

|                          | <i>Patients</i> |          |          |          |          |          |          |          |          |           |           |           |           |           |           |           | <i>Cut-off<br/>score</i> |          |
|--------------------------|-----------------|----------|----------|----------|----------|----------|----------|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|--------------------------|----------|
|                          | <i>1</i>        | <i>2</i> | <i>3</i> | <i>4</i> | <i>5</i> | <i>6</i> | <i>7</i> | <i>8</i> | <i>9</i> | <i>10</i> | <i>11</i> | <i>12</i> | <i>13</i> | <i>14</i> | <i>15</i> | <i>16</i> | <i>A</i>                 | <i>B</i> |
| Object naming            | 52              | 40       | 38       | 55       | 44       | 54       | 48       | 40       | 50       | 56        | 35        | 58        | 60        | 60        | 50        | 55        | 54                       | 55       |
| Figure naming            | 34              | 23       | 8        | 52       | 30       | 48       | 26       | 31       | 28       | 38        | 17        | 58        | 52        | 56        | 36        | 44        | 42                       | 46       |
| Tactile naming           | 52              | 43       | 45       | 54       | 39       | 56       | 41       | 43       | 51       | 54        | 45        | 56        | 53        | 60        | 22        | 50        | 43                       | 53       |
| Naming to<br>description | 52              | 50       | 52       | 51       | 48       | 54       | 34       | 57       | 50       | 51        | 40        | 58        | 54        | 60        | 40        | 57        | 52                       | 54       |

*A* = last control subject's score. *B* = penultimate control subject's score.



comparison with the object test and patients with a negative score exceeding  $-4$  as showing the opposite discrepancy. By computing the bidirectional nonparametric tolerance limits with beta content and gamma confidence (Guenther, 1972), it can be stated with confidence greater than 0.995 that 90% of the normal population will have difference scores ranging within the two cut-off points found in the sample.

Table 5 shows the difference found in PCA patients for each comparison pair and the cut-off points. Photograph naming stands out as the most impaired task: its scores were disproportionally lower in 7 patients with respect to object naming, in 7 patients with respect to tactile naming and in 7 patients with respect to verbal naming, while in just 1 (Case 15) the opposite dissociation was observed with respect to tactile naming.

TABLE 5. TEST SCORE DIFFERENCES IN PCA PATIENTS

| Pair-comparison                         | Patients |     |     |    |    |    |    |     |    |    |     |    |    |    |     |    |
|-----------------------------------------|----------|-----|-----|----|----|----|----|-----|----|----|-----|----|----|----|-----|----|
|                                         | 1        | 2   | 3   | 4  | 5  | 6  | 7  | 8   | 9  | 10 | 11  | 12 | 13 | 14 | 15  | 16 |
| Objects-<br>photographs<br>COS = 16 - 3 | 18       | 17  | 30  | 3  | 14 | 6  | 22 | 9   | 22 | 21 | 18  | 0  | 8  | 4  | 14  | 11 |
| Objects-<br>tactile<br>COS = 14 - 3     | 0        | -3  | -7  | 1  | 5  | -2 | 7  | 3   | -1 | 2  | -10 | 2  | 7  | 0  | 28  | 5  |
| Objects-<br>verbal<br>COS = 6 - 4       | 5        | -10 | -14 | 4  | -4 | 0  | 14 | -17 | 0  | 5  | -5  | 0  | 6  | 0  | 10  | -2 |
| Tactile-<br>photographs<br>COS = 7 - 8  | 18       | 20  | 37  | 2  | 9  | 8  | 15 | 12  | 22 | 19 | 28  | -2 | 1  | 4  | -14 | 6  |
| Verbal-<br>photographs<br>COS = 14 - 4  | 13       | 27  | 44  | -1 | 18 | 6  | 8  | 26  | 23 | 16 | 23  | 0  | 2  | 4  | 4   | 13 |
| Tactile-<br>verbal<br>COS = 13 - 5      | 5        | -7  | -7  | 3  | -9 | 2  | 7  | -14 | 1  | 3  | 5   | -2 | -1 | 0  | -18 | -7 |

COS = cut-off score.

Object naming was disproportionally poorer with respect to verbal naming in 4 patients and to tactile naming in 2. A discrepancy in the opposite direction, however, was shown by 2 patients in the former comparison and by 1 in the latter. Five patients showed a much poorer performance on the tactile test than on the verbal test.

Four alexic patients could be retested on reading and naming six to twelve months after the first examination. Alexia was unchanged in 1 (Case 2), while it had improved in the other 3 (Cases 5, 8 and 11), although being still of such a degree as to make reading faulty and difficult. Naming scores (Table 6) followed

TABLE 6. NAMING SCORES AT THE SECOND EXAMINATION IN 4 ALEXICS

|                          | Case 2  | Case 5   | Case 8   | Case 11  |
|--------------------------|---------|----------|----------|----------|
| Post onset time (months) | 12      | 6        | 8        | 12       |
| Object no.               | 40 (0)  | 55 (+11) | 58 (+18) | 52 (+17) |
| Photograph no.           | 31 (+3) | 45 (+15) | 50 (+19) | 35 (+18) |
| Tactile no.              | 45 (+2) | 56 (+17) | 54 (+11) | 55 (+10) |
| Verbal no.               | 47 (-3) | 53 (+5)  | 60 (+3)  | 55 (+15) |

Gain since first examination in brackets.

the same pattern: no gain in Case 2, a substantial increase in the other patients. Case 8 performed in the normal range on all tests, Case 5 was still defective on photographs and Case 11 on both photographs and objects. It is worth mentioning that Case 7 had first been examined twelve months after the stroke and was severely impaired on all tests.

### *Intertest correlations*

The correlation of reading with the other naming tests was computed with Spearman's rank order coefficient ( $\rho$ ) as the distribution of reading scores was skewed. The ranking of the reading performance was essentially based on the total of word test scores, supplemented in tied cases by the letter score and, if necessary, by sentence score, that of colour on the total of naming and pointing scores and that of visual naming on the total of object and photograph scores. As shown in

TABLE 7. CORRELATIONS OF READING WITH NAMING TESTS (SPEARMAN'S  $\rho$ )

| Colour | Visual | Tactile | Verbal |
|--------|--------|---------|--------|
| 0.82*  | 0.93*  | 0.53**  | 0.31   |

\*  $P < 0.001$ ;      \*\*  $P < 0.05$ .

Table 7, the correlation of reading with visual naming was almost perfect (0.93), that with colour scores very high (0.82), that with tactile naming lower but still significant (0.53), while that with verbal naming (0.31) fell short of the significance level.

Table 8 shows the correlations between the four naming tests that used the same

TABLE 8. CORRELATIONS BETWEEN THE NAMING TESTS (PEARSON'S  $r$ )

|             | Photographs | Tactile | Verbal  |
|-------------|-------------|---------|---------|
| Objects     | 0.88*       | 0.53*** | 0.41    |
| Photographs |             | 0.51    | 0.52*** |
| Tactile     |             |         | 0.69**  |

\*  $P < 0.001$ ;      \*\*  $P < 0.01$ ;      \*\*\*  $P < 0.05$ .

set of 30 objects. It is worth noting the highly significant correlation not only of objects with photographs, which was easily predictable, but also of verbal naming with tactile naming. These were parametric correlations (Pearson's  $r$ ) and thus cannot be compared directly with the rank order correlations of Table 7.

### *Verbal memory*

Table 9 shows the patients' scores on the three verbal memory tests and the criterion values used to ascertain the presence of amnesia. Case 3 refused to take the test and Case 7 was discharged before testing. Case 14, who was left-handed, failed below the cut-off score on just one test, 4 patients (Cases 2, 9, 12 and 16) failed on two tests, the remainder failed on all three tests. Of the 4 nonalexics 1 was Case 14, 1 (Case 12) was impaired on two tests and 2 (Cases 4 and 13) were impaired on three tests.

TABLE 9. VERBAL MEMORY SCORES

|                                                  | <i>Patients</i> |     |   |     |     |     |   |     |     |     |     |     |     |      |     |       |
|--------------------------------------------------|-----------------|-----|---|-----|-----|-----|---|-----|-----|-----|-----|-----|-----|------|-----|-------|
|                                                  | 1               | 2   | 3 | 4   | 5   | 6   | 7 | 8   | 9   | 10  | 11  | 12  | 13  | 14   | 15  | 16    |
| Story recall<br>(crit. 15.8)                     | 1               | 4.9 | — | 3.9 | 6.3 | 9.8 | — | 7   | 0.2 | 0   | 1   | 8.2 | 8.3 | 20.6 | 8.3 | 4.64  |
| Ten-word<br>learning<br>(crit. 6.6)              | 4.9             | 7.4 | — | 5.5 | 4.5 | 5.7 | — | 5.5 | 6.7 | 2.7 | 2.7 | 7.5 | 4.6 | 7.6  | 3.6 | 5.72  |
| Paired-<br>associated<br>learning<br>(crit. 8.7) | 2.5             | 3.8 | — | 1.6 | 3.6 | 1.3 | — | 3.4 | 4.4 | 0   | 0   | 7.4 | 3.4 | 7.4  | 4.3 | 10.14 |
| No. of tests<br>failed                           | 3               | 2   | — | 3   | 3   | 3   | — | 3   | 2   | 3   | 3   | 2   | 3   | 1    | 3   | 2     |

— = test not given.

### *CT scan findings*

A CT scan was carried out from ten to forty days poststroke, except in 3 patients (Cases 3, 6, 7 and 16) in whom the interval from the onset of disease was 6, 3 and 12 and 3 months, respectively. Films of consecutive 9 mm thick cuts, parallel to the orbitomeatal line, were obtained and were identified using the pineal (P) slice as the reference and terming those below it P-1, P-2 and so on and those above, P+1, P+2, etc. (McAuley and Ross Russell 1979). The involvement of the following structures was determined, based on standard CT scan atlases: fusiform gyrus, lateral occipital (O3) gyrus, lingual gyrus, parahippocampal gyrus, cuneus, precu-

TABLE 10. CT SCAN SLICES SHOWING INFARCT

| Case | P-3 | P-2 | P-1 | P | P+1 | P+2 | P+3 | P+4 |
|------|-----|-----|-----|---|-----|-----|-----|-----|
| 1    |     | +   | +   | + |     |     |     |     |
| 2    |     | +   | +   | + | +   |     |     |     |
| 3    |     |     | +   | + |     |     |     |     |
| 4    |     | +   | +   |   |     |     |     |     |
| 5    |     | +   | +   | + | +   | +   |     |     |
| 6    |     | +   | +   | + | +   | +   | +   |     |
| 7    |     |     | +   | + | +   |     |     |     |
| 8    |     | +   | +   | + | +   | +   | +   | +   |
| 9    |     |     |     | + | +   | +   |     |     |
| 10   | +   | +   | +   | + | +   | +   |     |     |
| 11   |     |     |     | + | +   | +   | +   |     |
| 12   |     |     |     |   | +   | (+) |     |     |
| 13   |     |     |     | + | +   | +   | +   |     |
| 14   |     |     | +   | + |     |     |     |     |
| 15   |     |     |     | + | +   | +   |     |     |
| 16   |     |     |     |   | +   | +   | +   |     |

(+) minimal involvement of the slice.

neus, splenium, forceps major. The anatomical structure represented at slice P are the lingual and the parahippocampal gyrus and the calcarine fissure. They are also present at P-1, while the hippocampus and the fusiform gyrus are found at P-2. Upper slices show the forceps major, the splenium, the cuneus and the precuneus.

As indicated in Table 10 all alexic patients except Case 16 (who was mildly impaired) showed a low density area involving slice P. Of the 3 nonalexical right-handed patients only 1 (Case 13) had a lesion at slice P. Slice P+1 also was frequently involved, but since it was intact in Case 3, who was a severe alexic, and damaged in 2 nonalexical right-handed patients, its association with alexia seems less close than that of slice P. Cases can be divided into those with a lesion extending inferiorly (slice P and/or lower slices), those with a lesion extending superiorly (slice P and/or upper slices) and those where both the slices inferior and those superior to slice P were involved. Their number was 4, 5 and 7, respectively. Of the 6 alexics who scored 0 on the two-word reading tests 1 (Case 3) had inferior damage, 2 (Cases 9 and 11) superior damage and 3 (Cases 2, 5 and 6) damage extending to the inferior and superior slices.

It must be pointed out, however, that the correlation between the extent of the damage and the clinical picture is far from perfect. For instance, the extent of the lesion was much smaller in Case 7 (fig. 1), who was a severe alexic, than in Case 10 (fig. 2), who was mildly impaired.

## DISCUSSION

The findings of this study point out the rich gamut of neuropsychological symptoms associated with left PCA infarction and emphasize the advantage that accrues from investigating systematically the brain-damaged patients' performance

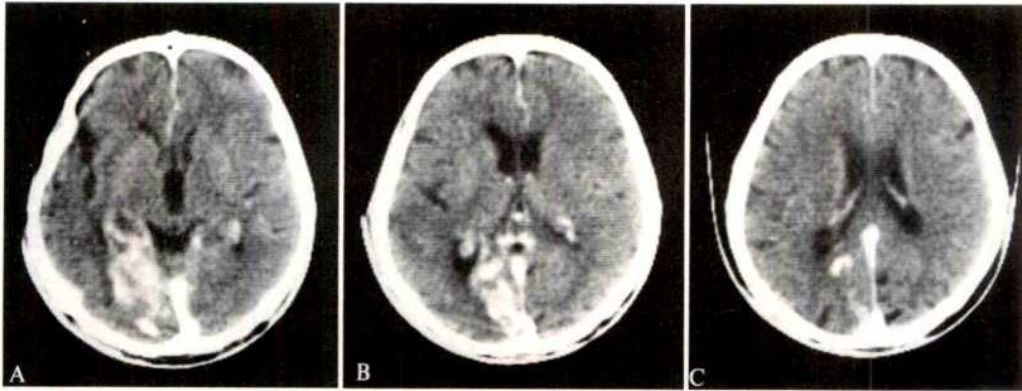


FIG. 1. CT scan slices P-1, P and P+1 for Case 7, a severe alexic.

with quantitative tests, which base the diagnosis on the score distribution of a large control sample. We will discuss the bearing of the data on the different elements of the clinical picture.

#### *The mechanism of pure alexia*

Alexia without agraphia was a very frequent, albeit not invariable, symptom in the present series of 16 consecutive patients: it occurred in 12 patients (75%), and was mild in 2 of them. When present, its features were typical, namely, individual letters were often not recognized, errors in word reading showed visual similarity with the target word and writing was remarkably better than reading. This study had clinical purposes and did not aim at investigating the linguistic aspects of dyslexia, which would have required a much more detailed testing of reading abilities. Suffice it to say that no patient conformed to the picture of spelling dyslexia (Warrington and Shallice, 1980). Of the 4 patients without alexia, 1 (Case 14) was left-handed. The other 3 patients were right-handed without a history of familial sinistrality. In 1 of them (Case 12), the size of the infarct was small and practically restricted to P+1, with only minimal involvement of P+2. In another (Case 4) the lesion was confined to P-2 and P-1 and did not encroach on P. In the third patient (Case 13), however, the lesion involved four slices (from P to P+3) and was practically superimposable to that of Cases 3, 9, 11 and 15, who presented with marked alexia. The absence of alexia in this patient defies any convincing interpretation. Also difficult to explain is why Case 10, who had a lesion extending from P-3 to P+2, was only mildly alexic (fig. 2).

CT scan evidence indicates that the slice most often involved by the infarct was slice P. Only 3 patients (Cases 4, 12 and 16) did not evince a low density area at this level: 2 were not alexic and 1 mildly alexic. The visual association cortex represented in slice P is the lingual gyrus, and our data, therefore, agree with those of Hoff *et al.* (1962) in stressing the relevance of its damage to reading impairment. Its crucial role is further supported by 2 cases of alexia (Cases 1, 3) in whom the



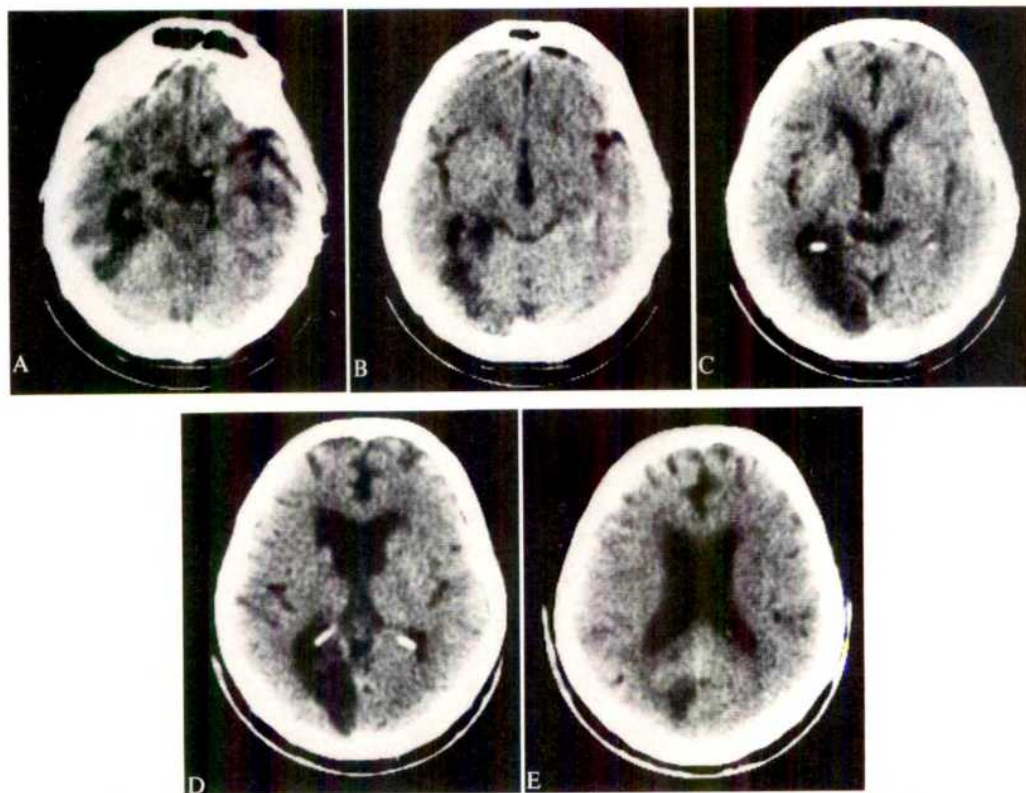


FIG. 2. CT scan slices P-2, P-1, P, P+1, P+2 for Case 10, who showed only mild signs of dyslexia.

infarct did not involve the splenium and/or the forceps major, because they suggest that the pathways transmitting visual information from the right visual association cortex do not run directly to the left angular gyrus, as envisaged by some authors, but, in accordance with Flechsig's rule, must first stop in the homologous areas of the left occipital lobe. It follows that, as pointed out by Orgogozo *et al.* (1979), Damasio and Damasio (1983) and Greenblatt (1983), the splenial damage is not a necessary component of the lesion pattern underlying pure alexia associated with right hemianopia, since the transcallosal pathways may be interrupted at any point of their course to the left visual association area.

The emphasis given to the bearing of the lingual gyrus on alexia is not meant to exclude the participation of other associative areas of the left medial occipital lobe in the processing of written symbols, and in fact a certain degree of recovery usually obtains also when the lingual gyrus is destroyed, although not to the point of making reading an easy and practised activity. The most severely impaired patients of our series were scattered in all three groups of lesion extending inferiorly and/or superiorly to P1, which suggests that the alexic picture is aggravated by the involvement of the neighbouring areas, without any marked difference between

them. The role of the fusiform gyrus has been already recognized by Potzl (Hoff *et al.*, 1962) and Greenblatt (1973), while that of the cuneus is disputed by some authors (Foix and Masson, 1923) and supported by others (Kurachi *et al.*, 1979). We submit that its damage concurs to make alexia worse, though being probably insufficient to disrupt reading, if the lingual gyrus is spared (Marie and Crouzon, 1900). More data are needed definitively to settle the issue.

### *Visual naming*

The traditional concept of pure alexia contrasts the disruption of reading with the preservation of other language and perceptual functions, the only exception being represented by the impairment in associating a colour with its name. The present data question this selective deficit and point out that, provided object and figure naming is assessed with the same accuracy as naming of letters and colours, a certain degree of visual naming impairment is present in practically all patients who have alexia. The correlation between the reading performance and the scores achieved on the other visual naming tests is impressive, ranging from 0.82 for colours to 0.93 for objects and photographs. None of the patients who read normally failed in naming colours, objects and photographs. Of the patients with reading difficulty, only 2 (Cases 10, 16) were not impaired on colour and object naming and they were mildly alexic. Both fell below the cut-off score on photograph naming, a test which was performed in the normal range by only 1 alexic (Case 6). If not the frequency, the severity of the deficit was greater for photographs than for objects, with 7 alexic patients showing a discrepancy between the scores of the two tests exceeding that found in any control subject.

This pattern of impairment is in keeping with the proposal of Oxbury *et al.* (1969) that all kinds of visual input run through the fibre system connecting the two occipital lobes and become liable to deterioration following a lesion anywhere in the system. The extent of deterioration is, however, a function of the wealth of information transmitted by the stimulus. This is greater for objects than for pictures, possibly due to their tridimensionality and familiarity (Damasio *et al.*, 1979) and for pictures than for letters, which are more easily mistaken because of the similarity of their physical appearance. Consequently reading may be expected to deteriorate more than picture naming and picture naming more than object naming.

A difficulty with this hypothesis is represented by the few cases where reading was spared, while naming of other types of stimuli was impaired, for example, colours (Mohr *et al.*, 1971) or objects (Albert *et al.*, 1975). Some authors have speculated that discrete fibre bundles and occipital areas are specialized in the transmission and processing of different kinds of visual material, and that the pattern of deficit depends on the location of lesion. The lingual and fusiform gyri have been proposed as the neural substrate of reading (Gloning *et al.*, 1966; Greenblatt, 1973), the anterior part of the lingual gyrus as that of colour naming (Damasio and Damasio, 1983), the cuneus as crucial for objects (Kurachi *et al.*,

1979). It is doubtful whether the available evidence is sufficient to draw reliable generalizations.

The finding that object and figure naming is regularly impaired in alexics contributes to solving the riddle posed by cases of optic aphasia and associative agnosia, which are contingent on damage of approximately the same cerebral structures as those responsible for alexia. These cases are less puzzling if they are considered at the end of a continuum ranging from mild to severe deterioration in the transmission of visual input to language centres, possibly as a function of the extension of the lesion. The whole gamut of impairment was found in our patients, at least 4 of whom (Cases 2, 3, 6, 11) showed a deficit in object naming comparable in severity with that of patients reported under the heading of optic aphasia or visual agnosia. The intimate nature of these two forms is a matter of debate, with some authors (Alexander and Albert, 1983; Larrabee *et al.*, 1985; Gil *et al.*, 1985) maintaining that they represent basically different symptoms, and others (Rubens, 1979) that they correspond to different stages of the same abnormality. Two (Cases 2, 8) of the 4 severe patients had a behaviour typical of optic aphasia in that there was almost always in their responses a hint to the circumstances or the way in which the object was used, revealing that recognition had been attained. The error pattern was different in the 2 other patients (Cases 3, 11), whose errors, mostly unrelated or of visual type, resembled those of visual agnosia. It is of interest that the error type may change in successive examinations, with visual agnosia giving way progressively to optic aphasia. This was seen in 1 of the optic aphasic patients (Case 8), who, when examined in the first ten days poststroke, showed a complete inability to identify an object even when he was requested to pantomime its use or to choose among verbal alternatives describing its use. The patient rolled his eyes and moved his head, trying to inspect the object from different angles, a behaviour that is considered typical of visual agnosia. Thirty days later his errors on the object and photograph naming tests were all descriptions of use, superordinate names, or semantically related paraphasias. In 1 of the 2 patients (Case 11) considered to have visual agnosia, there was a decrease of visual and unrelated errors (from 22 to 17) and an increase of verbal errors (from 3 to 12) passing from the first examination, carried out nine days poststroke, to the second examination, carried out twenty days poststroke. These data are supportive of Rubens' (1979) view that the difference between associative visual agnosia and optic aphasia is more a question of severity than of quality and that patients complying with the criteria for a diagnosis of the former disorder can evolve to optic aphasia when reassessed at a later stage.

#### *Tactile naming and naming to description*

The majority of alexic patients were impaired not only when naming involved the visual modality, but also when it was in response to the tactile or verbal presentation of the stimulus. There was no substantial difference between the number of patients failing in these conditions and those failing on visual naming,



when allowance was made for the fact that on tactile naming the last control patient was an outlier whose score was exceedingly poor. If on this test the cut-off score is set at the level of the last but one control patient, 10 alexics scored below it. As to naming to description, 8 alexics scored below the last control patient and 2 additional patients scored below the last but one. CT scan evidence was unequivocal in showing that the lesion was restricted to the territory of the PCA and that the lateral temporal and parietal lobe were spared not only by the infarct, but also by oedema. The latter could not, at any rate, account for the impairment shown by the 6 alexic patients (Cases 2, 3, 6, 7, 8, 16) whose examination took place more than a month postonset.

We propose that the naming impairment can be accounted for by assuming that the language area could not avail itself of the visual representation of the object, due to the severance of its connections with the occipital lobe. The search for a name is likely to require a continuous exchange of information between the language centre and the associative cortices storing different memories of the stimulus and to be markedly hampered if the visual image of the object cannot concur to trigger its naming. The detrimental effect that the interaction between visual and naming centres may have on tactile naming has been pointed out by Beauvois (1982) in patients with optic aphasia.

#### *Verbal amnesia*

A deterioration of verbal memory performance was the symptom most frequently associated with left PCA infarcts. Every tested patient, alexic as well as nonalexical, was impaired on at least two of the three tests, with the exclusion of Case 14, who was left-handed and had in all likelihood verbal abilities shifted to the right hemisphere. Paired-associate learning scores and story recall were lower than the cut-off score in 13 of the 14 tested patients, and ten-word learning in 10 patients. The generality of memory impairment was paralleled by the frequency with which the hippocampal gyrus was damaged: only Cases 11 and 16 showed no low lucency in this area.

While the occurrence of a fully developed amnesic syndrome after bilateral PCA infarction is a well established clinical finding (Trillet *et al.*, 1980), there is only limited evidence that an infarct confined to the left side presents with memory impairment (Geschwind and Fusillo, 1966; Mohr *et al.*, 1971; Benson *et al.*, 1974; Caplan and Hedley-White, 1974; Boucher *et al.*, 1976; Kurachi *et al.*, 1979; Michel *et al.*, 1979). Our study strengthens this sparse evidence by documenting that impairment of verbal learning is a regular accompaniment of infarcts extending to the anterior territory of supply of the left PCA.

## CONCLUSIONS

The outcome of the present study shows that the scope of the neuropsychological functions disrupted after a left PCA infarct is wider than traditionally thought and encompasses in the majority of cases reading, visual naming of different kinds, naming elicited through nonvisual modalities, and verbal memory. Our data do not deny the possibility that single cases may show a striking dissociation in the ability of reading versus visual naming or of visual naming versus tactile and verbal naming, as has been repeatedly documented in the literature. It must be kept in mind, however, that these cases tend to be published because they exhibit the selective disruption of a specific ability and that, consequently, there is no guarantee that they represent the rule, rather than the exception. A reliable estimate of the consequences of a lesion to a given area can only be based on the systematic assessment of a series of consecutive patients, selected because that area was damaged. The only other study reporting the neuropsychological performance of a substantial number of patients is that of Damasio and Damasio (1983), but whose patients were selected for the presence of alexia and not for the presence of temporo-occipital damage. Out of 16 alexics, 2 had visual agnosia, 5 colour anomia and 2 memory deficits. However, the criteria used for making these diagnoses were not specified, and no test assessing colour naming and verbal memory was mentioned in the list of tests reported by this study.

Most of our patients were examined at an early stage of disease and any generalization on the long-term consequences of PCA infarcts would therefore be unwarranted. There were 2 alexic patients (Cases 3, 7) who were first tested six and twelve months, respectively, after the stroke and 2 other patients (Table 6) were retested at this time interval. All of them were dyslexic, though to varying degree. Five of them were impaired on photograph naming, 4 on object naming and 3 on tactile and verbal naming. It would appear that both alexia and anomia tend to improve with the passage of time, but that complete restoration of function is hard to achieve.

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# KNOWLEDGE OF MOTOR COMMANDS AND THE RECRUITMENT OF HUMAN MOTONEURONS

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## SUMMARY

This study examined the extent to which subjects can direct internal motor commands to specific pools of motoneurons. These commands were subthreshold for muscle activity and were presumably not associated with any change in background afferent activity. Percutaneous stimuli were delivered to the motor cortex using the technique of Merton and Morton (1980) while the discharge of the first-recruited motor units from two intrinsic hand muscles was recorded with selective needle electrodes. In the absence of movement or detectable electromyographic activity subjects learned to focus their internal command upon one of the pair of hand muscles such that a liminal cortical stimulus activated motoneurons in the 'focused' but not the 'unfocused' muscle. This ability was not acquired for pairs of muscles in the forearm. When the cortical stimuli activated only one motor unit in a muscle, the same unit was the first recruited during a voluntary contraction. These results suggest that motor commands can be precisely monitored and fractionated for individual intrinsic muscles of the human hand without recourse to afferent feedback. This ability may be useful for organizing and learning fine manipulative tasks.

## INTRODUCTION

Appropriate central signals or motor commands are generated before the onset of voluntary movement. Ultimately these commands are 'focused' to excite or inhibit specific populations of interneurons and motoneurons within the spinal cord. Changes in neuronal activity before movement are widespread (Deecke *et al.*, 1969), involving not only the motor cortex (e.g., Evarts, 1966; Tanji and Evarts, 1976; Lamarre *et al.*, 1983) but also the supplementary and premotor areas (Brinkman and Porter, 1979; Weinrich *et al.*, 1984), cerebellum (e.g., Thach, 1970, 1978), thalamus (Strick, 1976; Horne and Porter, 1980) and basal ganglia (e.g., DeLong, 1973; Ianssek and Porter, 1980; Georgopoulos *et al.*, 1983). However, little is known of the extent to which perceived motor commands can be directed to specific motoneuron pools in normal subjects when there is no change in background

afferent activity. The present study was designed to investigate the extent to which motor commands can be focused voluntarily on the intrinsic muscles of the hand.

Although central motor commands must be generated during voluntary muscle contraction, it is not clear whether subjects receive central feedback related to the efferent command itself (in addition to input from the limb). That is, do subjects have any knowledge related to the central motor outflow? Whether corollaries of such motor commands can generate specific sensations has been a contentious subject for over a century (e.g., Lewes, 1878; Waller, 1891; *see also* Sperry, 1950; von Holst, 1954; for reviews, *see* Goodwin *et al.*, 1972; McCloskey, 1981; Gandevia, 1987). There is now evidence which suggests that subjects have a conscious knowledge of the size (e.g., McCloskey *et al.*, 1974; Gandevia and McCloskey, 1977*a,b*, 1978; Cafarelli and Bigland-Ritchie, 1979; Jones and Hunter, 1983) and timing (McCloskey *et al.*, 1983; Libet *et al.*, 1983) of central motor commands and that this information gives rise to the sensation of heaviness or effort (for review, *see*, McCloskey, 1981). Evidence from patients with discrete cerebral lesions suggests that the former sensation may require neural traffic to, or from, the motor cortex (Gandevia, 1978, 1982, 1987; Hobbs and Gandevia, 1985). But even if it is accepted that there is conscious appreciation of internal signals related to central motor commands, it is not known to what extent this information is useful for modulation of motor outflow, for example, when learning a new task. Studies in monkeys deafferented at birth, or even in utero, suggest that learning can take place in the absence of any peripheral afferent information from the limbs (Taub, 1976; *see also* Knapp *et al.*, 1963; Bossom, 1974; Polit and Bizzi, 1979). This implies that the animals have some knowledge of internal motor commands and that these provide accurate information as to the size and extent of the motor outflow. Comparable studies in man are rare (Lashley, 1917; Nathan and Sears, 1960; Volpe *et al.*, 1979; Rothwell *et al.*, 1982; Sanes *et al.*, 1985). A patient with severe peripheral deafferentation of the hands and forearm was able to learn only relatively simple tasks (Rothwell *et al.*, 1982); for example, he learned to flex his thumb rapidly through three different angles without vision, yet he was unable to learn to drive a new car.

The present experiments examined the learning of central motor signals in normal man. Subjects learned to focus a subthreshold motor output onto one muscle of a pair such that the central excitability of the neurons which controlled that muscle was greater than that of the other. To test the excitability of the relevant pools of motoneurons, percutaneous stimulation of the motor cortex was used (Merton and Morton, 1980). The results provide further evidence that subjects have conscious knowledge of their internal motor commands, and that this provides accurate information of the level of muscle contraction and the muscles involved. Our findings suggest that such internal signals might contribute to learning of a task which provides no peripheral sensory feedback to the CNS. A brief report of some of these results has been presented (Gandevia and Rothwell, 1986).

## METHODS

Nine experiments were performed in 4 subjects (including the authors). The procedures used were approved by the institutional ethics committee. Subjects sat in a comfortable chair with the forearm and hand resting on a padded table.

### *Stimulation and recording technique*

Corticofugal volleys were elicited using the technique of percutaneous cortical stimulation (Merton and Morton, 1980). Stimuli were delivered to the motor cortex through two electrodes fixed to the scalp with collodion. The cathode was at the vertex, and the anode 7 cm lateral to it. The stimulator (Digitimer D180) was used to deliver single stimuli of 200–500 V (time constant 50  $\mu$ s). In the first series of experiments, needle electrodes (bifilar or concentric) were inserted into two intrinsic muscles of the hand, usually abductor pollicis brevis and abductor digit minimi or the first dorsal interosseous, and positioned to record from the earliest-recruited motor units in each muscle. Multiple passes through each muscle were made to ensure that the recording needle was focused on the units first recruited in a voluntary contraction. In these muscles the needles recorded at least three discrete single motor unit potentials during weak voluntary contractions of less than 2% maximum. Signals from the two muscles were amplified (160 Hz – 3.2 kHz), and shown continuously to the subject on a large oscilloscope which was not triggered by the cortical stimuli. In addition, the signals were processed by separate audio amplifiers and played over loudspeakers throughout the study. The EMG signals were also monitored by an experimenter at high gain using a digital oscilloscope with a pretriggering facility. This oscilloscope was triggered only by the cortical stimuli and was not viewed by the subject until after the individual trials. Surface electrodes at high amplification were also used to record any muscle activity that was not picked up by the needle electrodes. This signal was also displayed to the subject and the experimenter on a third oscilloscope. In the second series of experiments, similar techniques were used to study pairs of forearm muscles. Both muscles in each pair were flexors or extensors. Common pairs included flexor carpi ulnaris and flexor carpi radialis, extensor indicis and a digital component of extensor digitorum communis, or extensor carpi radialis and extensor carpi ulnaris. At least two such pairs were studied in each experiment.

Comfortable positioning of the forearm and hand allowed the subject to relax the required muscle groups. After the intramuscular electrodes had been positioned, the intensity of the contralateral cortical stimulus was adjusted so that it was at, or just below, the level required to activate a few motor units in both muscles when the hand was relaxed. In some preliminary trials the stimulus failed to activate motor units in either muscle. Subjects were then asked to 'focus attention' or 'concentrate their effort' on one of the muscles such that the cortical stimulation evoked a muscle action potential in the 'focused' but not the 'unfocused' muscle. The subjects were not told how this was to be done but they were asked to avoid any deliberate rapid movements which involved the test muscle at a time that the cortical stimuli may have been anticipated. Subjects were allowed to prepare to contract the test muscle but were not permitted to recruit motor units in any of the monitored muscles. Subjects were asked to report any particular experimental strategies which they found effective. A specific requirement was that both muscles remained electromyographically silent for at least 5–10 s before any cortical stimulus. Single cortical stimuli were delivered at unpredictable times after the relevant muscles were quiescent. Subjects were initially told which muscles had been activated by the cortical stimulus and often viewed the triggered oscilloscope operated by the experimenter. Auditory feedback provided no information about the success or failure of a particular trial because it contained the 'click' artefact produced by the cortical stimulus. Once the ability to activate each of the muscles selectively following the stimulus had been acquired, subjects did not require further information about their performance, at least for a further 5–10 stimuli. Sequences were recorded on tape to allow comparison of the motor unit potentials recruited by the cortical stimuli and voluntary activity and for measurement of the latency of single units following the cortical stimuli.

Development of the ability to activate differentially the pair of muscles was assessed by monitoring

the success or failure of each trial. In successful trials there was evoked activity in the 'focused' but not the 'unfocused' muscle and in unsuccessful trials there was evoked activity in the unfocused but not the focused muscle. For statistical analysis those trials in which the cortical stimuli activated motor units in both muscles or failed to activate units in either muscle were discounted. This eliminated 10–35% of trials among the different subjects. The probability of obtaining the remaining successes and failures was analysed with a two-sided sign test. Statistical significance was accepted at the 5% level.

## RESULTS

### *Selective activation of muscles*

The needle electrodes were initially positioned to record the earliest-recruited motor units in each muscle. With the subjects completely relaxed, the strength of the cortical stimulus was adjusted to be at, or just below, that required to produce a liminal twitch involving two or three motor units in each muscle. Subjects were then instructed to 'focus' their 'effort' or 'attention' on one of the muscles (*see Methods*), so that the cortical stimulus evoked activity only in the muscle specified. Cortical stimuli were delivered during the periods of attempted focusing at unpredictable times, at least 5 to 10 s after both muscles became electromyographically silent. After periods between 5 min and 1 h, all subjects were able to 'focus' a subthreshold motor command such that when the hand muscles were electrically silent, and without any change in the posture of the hand, cortical stimulation activated only the muscle under test. Subjects were then able to change their commands so that the other (previously silent) muscle was activated by the same cortical stimulus. Sequences for hand muscles were usually terminated by at least 6 consecutive cortical stimuli which activated only the required intrinsic muscle. At this stage the subjects could usually predict accurately the occurrence of successful trials.

Figs 1 and 2 show results from an experimental sequence in 1 subject. In 6 of the 21 trials shown in fig. 2 the cortical stimulus either failed to activate any motor units (5 trials) or activated units in both muscles (1 trial). However, in the remaining 15 trials the motor cortical stimulus only activated motor unit(s) in the focused muscle. In each subject this ability to activate the motoneuron pools differentially was statistically significant ( $P < 0.01$ ).

In similar sequences subjects were also able to activate *both* or *none* of the muscles following the cortical stimuli. Presumably this reflects the well-known ability of 'reinforcement' manoeuvres to alter spinal excitability and as such this ability was not relevant to the specific hypothesis under study, namely, that subjects can differentially control the subthreshold excitability of various muscles.

Subjects were not uniform in their descriptions of the strategies used to focus upon one or other muscle. Usually they attempted to make a prolonged extremely weak 'effort' involving the focused muscle, at a level below that which activated motor units. All subjects reported that some deliberate concentration on the target muscles was required to maintain them in a state of readiness for the unpredictable



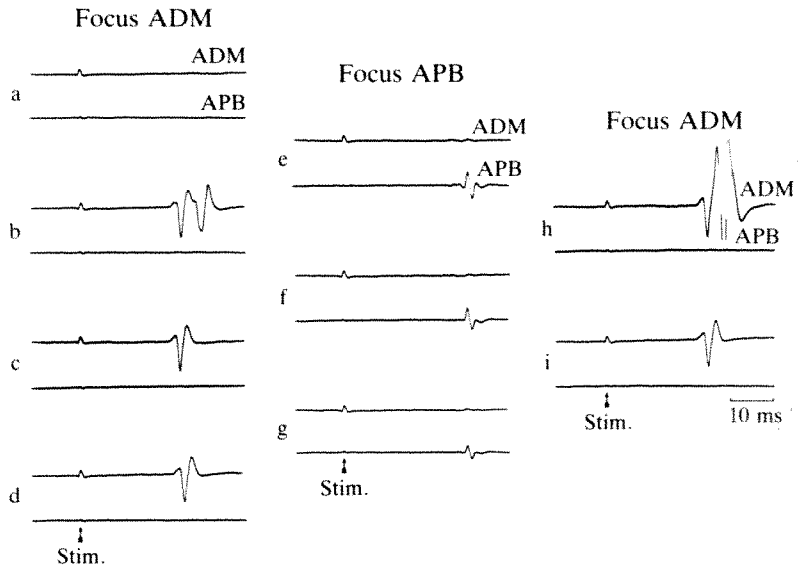


FIG. 1. Nine pairs of EMG recordings made with concentric needle electrodes from one continuous sequence of attempted 'focusing' in 1 subject. The *upper panel* in each pair is from abductor digiti minimi (ADM) and the *lower one* from abductor pollicis brevis (APB). Further data from this sequence are shown in figs 2 and 3. Arrows indicate the timing of stimuli to the contralateral motor cortex. The vertical calibration is  $100\ \mu\text{V}$  for both muscles.

In the first column (trials a-d), the subject focused on ADM. On the first trial (a), the cortical stimulus failed to evoke activity in either muscle. On the next three trials, the subject successfully achieved activity in ADM without discharging APB. The instruction was then changed to focus on APB. After 3 successful trials (e,f,g), the instruction was reversed again to focus on ADM (h,i). Note saturation of the response from ADM in trial h. These records are the raw data of the last 10 trials analysed in fig. 2.

cortical stimuli. After making a number of successful trials with each muscle the subjects often indicated to the experimenter the correct outcome of a particular trial (i.e., success or failure). Occasionally 2 subjects concentrated upon 'suppression' of the nonfocused muscle. This strategy was used in two unsuccessful sequences in which the intensity of the cortical stimuli was too high as more than three motor units were sometimes activated in the nonfocused muscle. Whatever effective strategy was ultimately developed, it involved no movement of the wrist and fingers or detectable electromyographic activity in the monitored muscles. As the posture of the hand was unaltered during the period before the stimuli were delivered, a change in background activity of receptors in skin, joint or muscles was unlikely (see Discussion).

The same subjects were *unable* to focus accurately upon pairs of flexor or extensor muscles in the forearm when studied on a subsequent occasion despite a prolonged period of training (3-4 h). The reported frustration at such attempts was often accompanied by difficulty in learning to recruit the required muscle in isolation during a voluntary effort. This was particularly notable for the ulnar and radial flexors or extensors of the wrist.

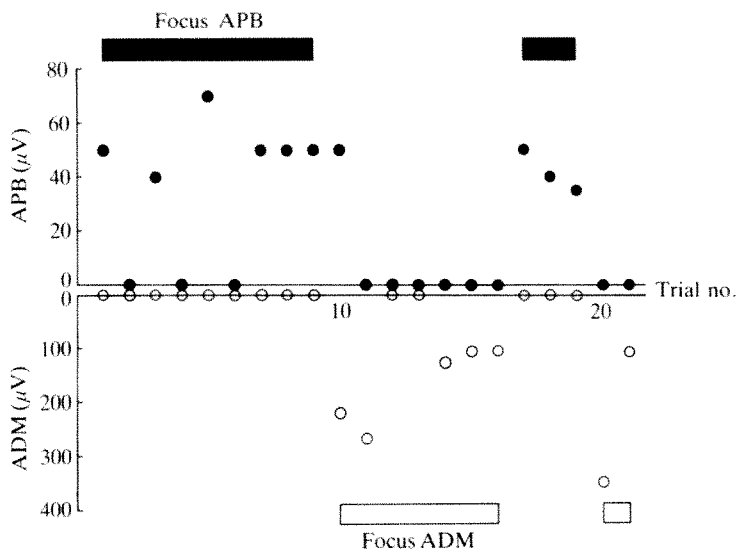


FIG. 2. Summary of data from a complete experimental sequence (*see also* fig. 1). Trials in which the subject was required to focus on abductor pollicis brevis (APB) and abductor digiti minimi (ADM) are shown by filled and unfilled bars, respectively; 21 trials are shown, beginning with the instruction to focus on APB. On each trial, the peak-to-peak size of the potential evoked in each muscle has been measured, with APB plotted upwards and ADM downwards. The size of the first-recruited motor unit was 40–50  $\mu\text{V}$  in APB, and 100  $\mu\text{V}$  in ADM. Potentials larger than this were composed of more than one motor unit. On all trials, the motor cortical stimulus evoked a larger muscle action potential in the focused than the unfocused muscle, although occasionally the stimulus failed to activate motoneurons in either muscle (trials 2, 4, 6, 12, 13) or activated motoneurons in both (trial 10).

### Motor unit recruitment

These experiments also provided an opportunity to examine the recruitment of motor units excited by stimuli to the motor cortex. When stimulation of the motor cortex produced a unitary muscle action potential in a particular forearm or intrinsic hand muscle, the same motor unit potential (as judged by the shape and size of the potential) was the first recruited during a voluntary contraction of that muscle. This is shown for three muscles from the same subject in fig. 3. This suggests that the corticospinal volley evoked by weak cortical stimulation excites the same low-threshold motor units as normal voluntary activity. A striking example of this is shown in fig. 3, in which voluntary activity often produced a 'doublet' firing of a single unit at the start of contraction (*see* Bawa and Calancie, 1983). The same 'doublet' also occurred in response to cortical stimulation. The latency for activation of single motor units was relatively long. For the data from 1 subject shown in fig. 3, for example, the latency for abductor digiti minimi was 22 ms, abductor pollicis brevis 28 ms and flexor carpi radialis 19 ms. By comparison, the minimal latency to larger twitches recorded from surface electrodes was shorter (abductor digiti minimi 17 ms, abductor pollicis brevis 18 ms, flexor carpi radialis 14.5 ms). It is possible that much of this difference is due to the slow peripheral conduction velocity of motor units recruited early in voluntary contractions (Freund *et al.*, 1975; Borg *et al.*, 1978; *see* Discussion). Similar findings were

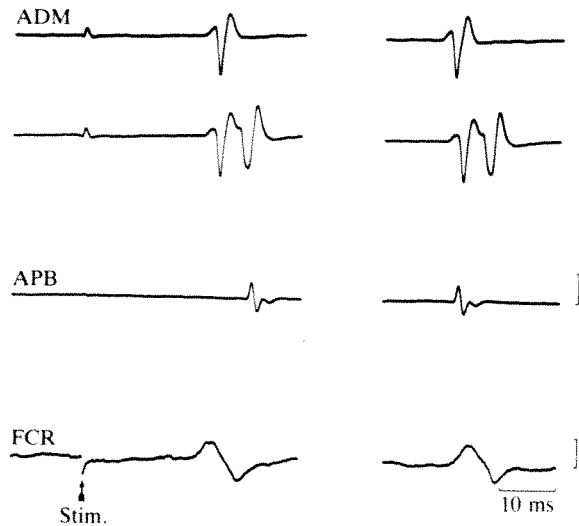


FIG. 3. Comparison of the first-recruited motor unit during a voluntary contraction (*right*) with that recruited by a liminal stimulus to the contralateral motor cortex (*left*). Recordings from the abductor digiti minimi (ADM; *upper two traces*), from abductor pollicis brevis (APB; *middle traces*) and from flexor carpi radialis (FCR; *bottom traces*) made with standard concentric needle electrodes. In ADM the same single motor unit potential was produced by cortical stimulation and by a weak voluntary contraction. This unit occasionally fired a 'doublet' in response to cortical stimulation and during a voluntary contraction (*second row of traces*). Similarly, for APB and FCR, the first-recruited motor unit potential in a voluntary contraction was the same as that recruited first by a cortical stimulus. The arrows indicate the timing of the cortical stimulus. Vertical calibration: 50  $\mu$ V for ADM and 40  $\mu$ V for APB.

observed in each subject. In one sequence, out of more than 20 in which recruitment of a single unit could be examined, two different motor units were activated by the cortical stimuli. However, these two low-threshold units (in flexor carpi ulnaris) also varied their order of recruitment during weak voluntary contractions so that this did not constitute an exception to the general finding that the cortical stimuli activated the motor units first recruited during a weak voluntary contraction. This observation has recently been extended to motor units in the intercostal muscles (S. C. Gandevia, unpublished observations).

## DISCUSSION

A major conclusion from the present results is that subjects can learn to activate a limited group of CNS neurons in the absence of any changes in peripheral feedback. Before the cortical stimuli were delivered, the hand did not move and no electromyographic activity was detected from electrodes within or overlying the muscles under study. Furthermore, a recent study has shown that following periods of biofeedback training for up to three hours, subjects do not acquire the ability to activate selectively the fusimotor system and so alter the discharge of spindle endings from the 'focused' muscle (Gandevia and Burke, 1985). Since the background activity from the hand did not change, the subjects must have been able to

monitor internal signals related to specific centrally-generated motor commands. The reasoning is as follows. During learning of the task the subject experiences a successful trial after a number of unsuccessful trials and is informed by the experimenter. For this trial, we cannot say whether success was achieved by chance or by conscious adjustment of the correct motor output. However, the experiment required the subject to repeat that initial success in subsequent trials. In the absence of any peripheral feedback (*see below*) the only way this could be achieved is for the subject to have had some knowledge of the size and destination of the successful motor output. Subjects were informed of successful trials and may even have felt the evoked muscle twitches, but this information provides no unique information about the size of the command itself at the time that the cortical stimulus was given.

It is not possible to be certain whether the motor commands which the subject learned to control represented excitation of the focused muscle, inhibition of the nonfocused one, or a combination of excitation and inhibition. However, there is circumstantial evidence to suggest that a combination of these influences operated during some sequences. Occasionally, one of the intrinsic muscles was preferentially activated by the cortical stimuli, presumably because the stimulus intensity was too high or the scalp electrodes were incorrectly positioned. The subject was then able to reduce the size of the evoked muscle action potential in the preferentially-activated muscle when he attempted to focus on the other muscle of the pair. The subject could learn to activate the latter muscle and to reduce, but not eliminate, the activation of the 'preferred' muscle. Thus, in the main study, subjects may have achieved success by suppressing many muscles with a general command (i.e., the opposite of a reinforcement manoeuvre) and then raising just one to threshold with an excitatory input. Subjects usually reported that they concentrated on making a liminal effort with the muscle for which focusing was requested.

It could be argued that since we did not record from all muscles of the hand or forearm that subjects might 'focus' their attention on a particular hand muscle by contracting a synergist in the forearm. This contraction would produce peripheral afferent feedback and might provide subliminal activation of the 'focused' muscle. For this to be an effective strategy, the contraction of the two synergistic muscles would always have to be linked. This does not usually occur. There will always be occasions when the synergist forearm muscle is contracted without activity in the hand muscle. Thus if the strategy of using overt contraction of forearm muscles is to work, the subject must know which particular synergy he is trying to achieve. In the absence of any afferent input from the intrinsic hand muscle in question, the only way this information can be obtained is from knowledge of signals related to the internal motor command. A similar line of reasoning can be used to counter, in part, the suggestion that the subjects may have intended or planned some other 'remote' motor act which, coincidentally or not, was associated with the initial successful motor output. Furthermore, subjects reported that no remote muscular contractions were deliberately attempted during the period before the cortical

stimuli were delivered. Finally, it is difficult to accept that such a strategy would permit the motor outputs to be swapped between two intrinsic muscles of the hand, particularly as this strategy apparently failed for more proximal muscles. Critical examination of the strategy of remote movement would require paralysis or deafferentation of all but the target pair of muscles.

Stimuli to the contralateral motor cortex were delivered at unpredictable times after the subject began to focus on one of the muscles and had maintained electromyographic silence in the required muscles for at least 5 to 10 s. This reduced the possibility that anticipation may have changed motoneuronal excitability and thereby explained the observed phenomenon. It also prevented the subject from initiating a rapid small contraction at the time the cortical stimulus was expected. Such a strategy was easily detected by a voluntary burst of electromyographic activity in the peristimulus period. This strategy (which was not permitted in the experimental sequences) may represent a special case of the phenomenon under investigation. The ramp of motor command was simply developed over a short period rather than being sustained over a number of seconds. This strategy may be related to the well-known ability of subjects to discharge a single action potential from a single motoneuron (e.g. Denslow, 1948; Basmajian, 1963; Kato and Tanji, 1972). This ability was confirmed in the present study for the motoneurons *first recruited* in voluntary contractions.

Not only do these results confirm previous suggestions that there exists internal knowledge of central motor commands (*see* Introduction), they also show that such knowledge is accurate enough to allow subjects to learn a task which demanded that activity of central neurons was (1) kept within a narrow range, such that the relevant motoneuron pool remained just below threshold, and (2) was directed towards specific groups of CNS neurons. Knowledge of central motor commands may subserve a number of discrete functions within the motor system (Gandevia, 1987).

Unfortunately, it is not possible to determine how the subthreshold command produced an overall facilitation of the pathway tested by cortical stimulation. As this form of stimulation preferentially activates a rapidly conducting pathway to motoneurons of intrinsic muscles of the hand (*see* Marsden *et al.*, 1983; Rothwell *et al.*, 1987; Day *et al.*, 1987), the facilitation may have occurred at the level of the cerebral cortex and/or at spinal levels. The electrical stimulus on the scalp has complex actions on cortical circuitry (Rothwell *et al.*, 1987; Day *et al.*, 1987). It may activate the axons of large corticospinal neurons at low stimulus intensities to produce a single efferent volley, and at higher intensities, the same efferent neurons may also be activated transsynaptically to discharge repetitively (Patton and Amassian, 1954). A change in cortical excitability produced in association with the 'subthreshold' motor commands may enhance the transsynaptic volleys and thus facilitate the muscle response (Day *et al.*, 1987). Alternatively, voluntary commands could activate central sensory neurons projecting onto motor pathways and thereby change motor excitability. We have no direct evidence for this latter possibility.

Changes in spinal motoneuron excitability may also be present during the task but, as H reflexes are not easily obtainable in the intrinsic muscles of the hand (see Buller *et al.*, 1980), we were unable to test this possibility. H reflexes have been used to document a number of changes in motoneuronal excitability which are associated with anticipation in the period following a warning signal and in the period prior to a movement (e.g., Gottlieb *et al.*, 1970; Pierrot-Deseilligny and Lacert, 1973; Coquery, 1978; Eichenberger and Rüegg, 1984). In our experiments, however, there was no specific warning of the cortical stimuli and they were delivered at unpredictable times. Furthermore, it is improbable that such strategies could produce differential facilitation of closely related muscles (Brunia and Vuister, 1979; Honore *et al.*, 1983). In addition, direction of attention to one leg does not produce differential enhancement in the amplitude of the H reflexes elicited in the focused triceps surae muscles at rest (S.C. Gandevia and J.C. Rothwell, unpublished observations).

The inability of subjects to focus their subthreshold commands onto one of a pair of forearm muscles was not due to unfamiliarity with the required task as subjects were tested with these muscle groups in separate studies after the capacity had been acquired for intrinsic muscles of the hand. It may reflect a more fundamental property of the corticospinal system: that is, the relatively small number of branches which a corticospinal axon makes to motor pools of distal muscles, as compared with the larger number of branches made to pools of proximal muscles (Shinoda *et al.*, 1979). This anatomical arrangement must contribute to the capacity of primates to fractionate motor commands to hand muscles (Lawrence and Kuypers, 1968; Muir and Lemon, 1983; *see also* Phillips and Porter, 1977). The present results therefore suggest that there is a difference in the supraspinal control of muscles in the human hand and forearm.

#### *Recruitment order of motoneurons*

Voluntary contraction of a muscle recruits motor units in intrinsic hand muscles in order of increasing size (Milner-Brown *et al.*, 1973) and axonal conduction velocity (Freund *et al.*, 1975; Borg *et al.*, 1978), as predicted by Henneman's size principle (Henneman *et al.*, 1965). Since the first unit recruited by a cortical stimulus was the same as that recruited in a voluntary contraction, it is tempting to suggest that cortical stimulation recruits motor units according to the same principle. Indeed, the long latency of single motor unit responses after cortical stimulation is consistent with the early recruitment of motoneurons with slowly conducting axons. Similar results have been obtained recently by Hess and Mills (1986) using the technique of magnetic cortical stimulation.

Interpretation of our observation may be complex. The order of motoneuron recruitment to stimulation may depend more on the bias given to motoneurons by the subthreshold motor command than to differences in the size of excitatory postsynaptic potentials (EPSPs) governed by the stimulus. Furthermore, delays caused by transsynaptic activation of motor cortical elements may contribute to

the long latency of the first units recruited by a cortical stimulus. There are few data from studies in subhuman primates which might help to resolve these problems. In a study in baboons, Clough *et al.*, (1968) examined the size of maximal monosynaptic (corticomotoneuronal) EPSPs elicited in motoneurons innervating forearm muscles after anodal stimulation of the exposed motor cortex. They found that among motoneurons of the median nerve, the EPSPs tended to be larger for cells with more rapidly conducting axons than for those with more slowly conducting axons. Among motoneurons supplying the extensor digitorum communis, the opposite tendency was found. It is clear that the question of the 'pure' corticomotoneuronal recruitment order has yet to be resolved.

In conclusion, the present results suggest that subjects can learn to fractionate subthreshold motor commands to intrinsic muscles of the hand without recourse to afferent feedback. It may be that this ability is of importance in the learning and control of fine manipulative behaviour which is so characteristic of the human hand.

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## CLINICAL AND PATHOLOGICAL FEATURES OF DIFFUSE CORTICAL LEWY BODY DISEASE (LEWY BODY DEMENTIA)

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### SUMMARY

Four patients with severe dementia and a parkinsonian syndrome are described. Dysphasia, dyscalculia, dyspraxia, visual and verbal memory disturbance and psychosis, usually of depressive type, occurred early in the course of the illness. Pathologically they were characterized by the presence of numerous Lewy bodies throughout both the cerebral cortex and brainstem. Three cases also had severe neurofibrillary tangle change or senile plaques in the neocortex, compatible with Alzheimer's disease, but the cortical tangle distribution did not always match that of the Lewy bodies. This disorder may form part of the spectrum of pathology in Parkinson's disease, where it may be one possible cause of dementia.

### INTRODUCTION

Bradykinesia and rigidity in idiopathic Parkinson's disease are due to degeneration of nigrostriatal neurons. Cell bodies in the substantia nigra are progressively lost and Lewy bodies develop within some of the remaining nerve cells. Neuronal degeneration with the formation of Lewy inclusion bodies also affects regions of the nervous system such as the locus coeruleus, dorsal motor nucleus of the vagus, hypothalamus, nucleus basalis of Meynert and sympathetic ganglia (Forno, 1982). The neuropsychological sequelae of Lewy body degeneration in these sites is unknown, but severe cell loss in the nucleus basalis of Meynert and autonomic nervous system is believed to cause neuropsychological impairment and autonomic failure, respectively. It is not generally appreciated that patients with Lewy bodies in the substantia nigra may also have Lewy bodies in the cerebral cortex (Oppenheimer, 1984; Heilig *et al.*, 1985). Forno (1969) found small numbers of Lewy bodies in the temporal cortex of 6 out of 50 individuals dying without Parkinson's disease, where Lewy bodies in the substantia nigra were an incidental finding at death. In a group of 21 patients with idiopathic Parkinson's disease, 2 had Lewy bodies in the temporal cortex and hippocampus (Forno, 1966, 1969). Jellinger and Grisold (1982) found that among 96 cases of Lewy body-Parkinson's

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disease, 10 had a few Lewy bodies in the cerebral cortex, often associated with Alzheimer changes and dementia.

Moderate or severe Lewy body disease in the cerebral cortex was in fact first reported by Helfand (1935) in Hallervorden-Spatz disease. 'Ball-like' inclusions were found in small pyramidal cells of the deeper cortical layers of a 25-year-old female. The clinical course was of dementia, a parkinsonian syndrome and cerebellar signs, and the globus pallidus was pigmented. Recently several Japanese neuropathologists have described patients with a parkinsonian syndrome and severe dementia (Kosaka *et al.*, 1984). In contrast to patients with small numbers of Lewy bodies in the temporal cortex (Forno, 1969; Jellinger and Grisold, 1982), these patients had moderate or large numbers of Lewy bodies in many parts of the cerebral cortex, as well as Lewy bodies in the brainstem. The pallidal degeneration and pigmentation of Hallervorden-Spatz disease were not reported and moderate or severe Alzheimer-type cortical changes were commonly found in addition to the Lewy bodies. Clinically diagnosed Alzheimer's disease may be associated with a mild parkinsonian syndrome (Pearce, 1974; Drachman and Stahl, 1975), but some cases of this kind might have cortical Lewy body disease. The present paper describes 4 cases of cortical Lewy body disease. It provides more detailed clinical and pathological information than is available in the literature and quantitative histological assessments of Alzheimer neurofibrillary tangles, senile plaques and Lewy bodies.

#### CASES AND METHODS

The 4 cases in this report were identified during a retrospective study of 47 cases of idiopathic Lewy body-Parkinson's disease, in which the cerebral cortex as well as the brainstem were available for examination. The brains and spinal cords (the spinal cords were available only in Cases 1 and 2) were fixed in 10% neutral formol saline for 4-6 weeks. The cerebral hemispheres were then cut into 1 cm coronal slices. Tissue blocks were taken from a variety of sites, including the superior frontal gyrus (Brodmann area 9), superior parietal gyrus (area 7), middle temporal gyrus (area 21), occipital pole (area 18) and the hippocampal and parahippocampal gyri. Coronal blocks of the nucleus basalis of Meynert were cut at the level of the posterior part of the optic chiasm. The brainstem was cut horizontally and blocks taken which included one at the level of the third nerve for the substantia nigra and one in the mid-upper pons for the locus coeruleus. A sample of the parahippocampal gyrus in Case 1 was postfixated in 1% osmium tetroxide, dehydrated and embedded in araldite. Ultrathin sections were stained with uranyl acetate/lead citrate and examined by electron microscopy. The samples of cerebral cortex, embedded in paraffin wax, were used to map the distribution of Lewy bodies at magnifications of  $\times 100$  and  $\times 400$ . Lewy bodies were counted in randomly chosen cortical areas in 12  $\mu$ m haematoxylin and eosin (H and E)-stained sections using an eyepiece graticule at a magnification of  $\times 400$ . Cortical and subcortical Lewy bodies were defined as eosinophilic cytoplasmic inclusions with a halo. Many cortical Lewy bodies were less well-defined than those in subcortical locations, because of their smaller size and less intense staining. Other inclusions frequently found in Parkinson's disease, which we have called pale bodies, do not stain using conventional techniques and lack a halo. Their distribution mirrors that of Lewy bodies. In the cerebral cortex they have a smooth texture, in the brainstem they are faintly granular. Pale bodies were not counted. Five adjacent sweeps of 0.33 mm width were made perpendicular to the cortical surface and a mean Lewy

body count was obtained from 6–10 sites in each cortical lobe, and from one site in each part of the hippocampus. In Case 2 cortical neurofibrillary tangles were counted in wax-embedded material (12  $\mu$ m), with a modification of the Palmgren method which enables tangles to be selectively stained (Cross, 1982). A total of 20 randomly selected graticule areas (0.11 mm<sup>2</sup>) were counted to obtain a mean tangle score for each lobe and for the parahippocampal gyrus and for each division of the subiculum. In Cases 3 and 4 frozen sections of temporal lobe were stained by the von Braunmuhl technique to show plaques. Plaque counts were made using wax-embedded material stained with Bielschowsky's method, in 10 randomly selected graticule fields at  $\times 100$  magnification (1.7 mm<sup>2</sup>), and a mean plaque score was obtained for each lobe. Paraffin wax-embedded sections from comparable levels of the substantia nigra and locus coeruleus were cut at a thickness of 10  $\mu$ m (Case 3) and 12  $\mu$ m and stained with H and E. Quantitative assessments of neuronal loss at a low power were supplemented by counts of pigmented cells at  $\times 400$  magnification in 1–4 sections. Differences in section thickness were corrected using Abercrombie's formula to a thickness of 12  $\mu$ m (Abercrombie, 1946). Other brain areas were examined using standard neuropathological techniques and a variety of stains.

Counts of pigmented cells and Lewy bodies in the substantia nigra were compared with those obtained from 15 brains of nondemented Lewy body-Parkinson's disease patients without cortical Lewy bodies (mean age 68.7 yrs). A second group of 20 brains from patients without neurological disease were used as normal controls (mean age 67.6 yrs).

## CASE HISTORIES

These are summarized in Table 1.

TABLE 1. CORTICAL LEWY BODY DISEASE: SUMMARY OF CLINICAL FEATURES

| Case | Sex | Age at onset<br>(yrs) | Duration of<br>disease (yrs) | Clinical features                                                                                                |
|------|-----|-----------------------|------------------------------|------------------------------------------------------------------------------------------------------------------|
| 1    | F   | 27                    | 3                            | Lethargy, somnolence, depression, paranoid delusions, parkinsonian syndrome, dysphasia, dementia, hallucinations |
| 2    | F   | 33                    | 5.5                          | Depression, parkinsonian syndrome, dementia, paranoid delusions and auditory hallucinations                      |
| 3    | M   | 56                    | 5.5                          | Topographical amnesia, dementia, dysphasia, dyscalculia, dyspraxia, mild parkinsonian syndrome                   |
| 4    | M   | 70                    | 3                            | Dementia, visual and auditory hallucinations, parkinsonian syndrome.                                             |

### Case 1

A 27-yr-old woman with no antecedent medical history or relevant family history became lethargic in May 1961, nine months after the birth of her second child. Six months later a psychiatrist noted insomnia, feelings of irritability and hatred, paranoid delusions and a decreasing concern for domestic responsibilities. She developed a rest tremor and rigidity of the right arm and leg. Within six months the tremor and stiffness had involved the left side. By December 1962, her sleep rhythm was reversed, her walking was slow and she was unable to rise from bed without risk of falling. A diagnosis of hysteria was made and a course of electroshock therapy given, after which she improved for a few days.

In March 1963 she was referred to the National Hospital for Nervous Diseases. On examination she lay in bed with eyes closed, talking in a high pitched monotonous voice. Neuropsychological

assessment showed a WAIS verbal IQ of 91 and a performance IQ of 74. The verbal test scores ranged from the average level for vocabulary to the borderline-defective level for digit span, a performance estimated to be well below her premorbid level. On nonverbal tests she scored at the average level on the Picture Completion test and at the defective level on two tests involving construction, the Block Design and Object Assembly. There was palilalia, echolalia and nominal dysphasia. There were frequent paraphasias and difficulty naming all but the most common objects. She had difficulty spelling simple words and a mild receptive dysphasia. Memory for recent events was poor and learning was impaired. She easily became agitated, when a pronounced rest tremor developed in both hands. There was blepharoclonus and facial hypomimia with an occasional fatuous smile. There was generalized poverty of movement with impairment of the ability to perform rapid alternating movements in the limbs and tone was increased with cogwheel rigidity.

An EEG showed mild diffuse abnormalities, but no localizing or diagnostic features. Alpha rhythm at 8 Hz was irregular and of low amplitude. It was partially obscured by a considerable intermixture of fast activity at 28 Hz maximal in frontal areas, but spreading widely. There were bilateral runs of theta waves at 6–7 Hz. A lumbar air encephalogram (AEG) showed marked frontal atrophy.

A diagnosis of postencephalitic parkinsonian syndrome was made and treatment with orphenadrine and benzhexol produced slight benefit. Over the next few months she adopted curious postures in which she sat or lay with her head and neck extended staring at the ceiling for long periods scarcely accessible to questioning, with sweating and limb tremor. Six months later she was readmitted to hospital because of paranoid delusions and visual and auditory hallucinations. At times she sat with her eyes closed and was apparently difficult to rouse, on other occasions she was affable and responded to commands. There was evidence of progressive intellectual deterioration (WAIS verbal IQ score 82, performance IQ score 67), with moderately severe dysphasia and her performance on tests of learning and memory declined. Bradykinesia and rigidity were marked, coarse tremor was present and pressure sores appeared. Repeat examination of the CSF was normal and the EEG record was unchanged. A further AEG showed progressive cerebral atrophy with an increase in the size of lateral and third ventricles and a marked increase in the degree of cortical atrophy, particularly in the frontal regions. She died from bronchopneumonia in February 1964, aged 30 yrs, after an illness lasting 3 yrs. Her two sons now aged in their twenties are healthy.

### *Case 2*

A 33-yr-old woman became depressed and irritable in May 1979, seven months after the birth of her second child. One month later she developed a rest tremor of the left hand. She failed to swing the arm when walking and the left leg started to drag. Six months later she had left-sided rigidity and bradykinesia. L-DOPA in combination with a peripheral decarboxylase inhibitor (Madopar) produced considerable improvement, but after four months she experienced freezing episodes, early wearing-off effects and left-sided L-DOPA-induced peak dose chorea. By February 1982 she was having frequent falls with start hesitation, peak dose orofacial chorea and severe end of dose deterioration. Her medication at this stage was doxepin, benzhexol, amantadine, and Madopar. Bromocriptine was then given and Madopar stopped without any improvement. Her posture had become severely flexed, her gait shuffling and there was early memory impairment. Six months later she had paranoid delusions and auditory hallucinations which temporarily remitted when bromocriptine and amantadine were replaced by Sinemet, but in the next few months these symptoms returned and intellectual deterioration continued. By May 1984 she was akinetic with severe rigidity and dementia. A CT scan showed diffuse cerebral atrophy. She died of pneumonia 5.5 yrs from the onset, in November 1984.

### *Case 3*

A 56-yr-old lorry driver presented in 1972. Eighteen months earlier he had found difficulty interpreting signposts. According to his wife he then became confused and often believed that she

had their bungalow on tow. He became unable to find his way around their home. When examined in 1972 he stated that the reason for not finding the toilet was that 'the lorries kept changing with 6-8 rooms in each so that I don't know whether to go under some rooms and over others'. He developed considerable memory impairment and tended to confabulate. He was able to recall the dates of the first World War but not those of the second World War and his knowledge of current events was poor. He was able to give the year and month, but not the date. He was dyscalculic and showed expressive and nominal dysphasia. He named a dressing gown, a dress suit and donkey jacket. He then attempted to put the dressing gown on his feet. He was mildly euphoric. On one occasion he attempted to leave the examination room through a drawer in the desk. There were coarse rest and postural tremors and some limb rigidity. His parents, who died in late age, were not consanguineous. He had 3 healthy siblings and a son and daughter aged 30 and 36 yrs. The EEG was dominated by bilateral slow activity with recurring sharp elements. An AEG showed slight ventricular dilatation and moderate cortical atrophy. He became unable to care for himself and developed pressure sores. He died of bronchopneumonia 4 yrs later, 5.5 yrs from the start of the illness.

#### *Case 4*

A 70-yr-old man presented in 1973 with acute urinary retention. His wife related that for one year he had become forgetful, slovenly and unable to recall names for common things. He had intermittent confusion with visual and auditory hallucinations and periods of aggressive behaviour. His behaviour on the ward was disturbed and because he had become impossible to manage at home he was placed in a long-stay hospital ward. One year later he developed a parkinsonian syndrome, with bradykinesia and postural instability. He tended to wander and was subject to falls. He became more immobile and died at the age of 73 yrs from bronchopneumonia.

### PATHOLOGICAL FINDINGS

#### *Case 1*

Autopsy (Table 2) revealed cachexia and bronchopneumonia. The brain showed widening of frontal lobe sulci and slight enlargement of the third ventricle. There was depigmentation of the substantia nigra and locus coeruleus. Microscopic findings were of neuronal degeneration and Lewy body formation in areas characteristically involved in Parkinson's disease including the substantia nigra, locus coeruleus, dorsal motor nucleus of the vagus, nucleus basalis of Meynert and hypothalamus. In the substantia nigra there was moderately severe cell loss, as in the Lewy body-Parkinson's disease control group (26% of the mean normal control value). The substantia nigra pars reticulata was normal. The paranigral nucleus and central linear nucleus of the ventral tegmental area were severely involved. Cell loss in the locus coeruleus was of moderate severity, but only mild in the nucleus basalis and the dorsal motor nucleus of the vagus. There were large numbers of axonal swellings and spheroids in the nucleus gracilis and cuneatus; some of these showed target-like appearances and one Lewy body was present in the nucleus cuneatus. In the striatum there were eosinophilic axonal swellings in the putamen and to a lesser extent in the caudate nucleus, and axonal swellings in the region of the nigrostriatal tract. There was no abnormal pigmentation or iron deposition in the globus pallidus. The intermediolateral nucleus of the spinal cord contained axonal swellings, but no Lewy bodies.

TABLE 2. BRAIN WEIGHTS AND CELL COUNTS\* IN 12  $\mu$ m SECTIONS OF SUBSTANTIA NIGRA

|                  | <i>Brain weight<br/>(g)</i> | <i>Severity of cell loss<br/>in substantia nigra</i> | <i>Cell count</i> | <i>Cell count with<br/>Lewy bodies</i> |
|------------------|-----------------------------|------------------------------------------------------|-------------------|----------------------------------------|
| Case 1           | 1300                        | Moderate-severe                                      | 278               | 12                                     |
| Case 2           | 1230                        | Severe                                               | 72                | 22                                     |
| Case 3           | 1285                        | Moderate                                             | 483.5             | 23.2                                   |
| Case 4           | 1105                        | Moderate-severe                                      | 267               | 21                                     |
| Parkinson's      | 1055-1405 M                 | Moderate                                             | 289.2             | 15.4                                   |
| disease controls | 1080-1525 F                 |                                                      | (156-417)         |                                        |
| (15)             |                             |                                                      |                   |                                        |
| Normal           | 1140-1549 M                 |                                                      | 1061.6            | None                                   |
| controls (20)**  | 1060-1507 F                 |                                                      | (695.1-1573.2)    |                                        |

\*Cell counts obtained from 1-4 half-midbrain sections. \*\*Mild cell depletion was present in 5 normal controls. M = male. F = female.

In the cerebral cortex Lewy bodies were found in profusion in the deeper cortical laminae of all lobes, but they were less frequent in the subiculum and not found in the hippocampus. There were also many pale bodies. The occipital lobe contained axonal spheroids in deep cortical layers and in the adjacent white matter. There were no tangles or plaques.

### Case 2

At autopsy (Table 2) the body was emaciated and there was acute bilateral pyelonephritis. The brain did not show obvious atrophy, the only macroscopic findings being severe depigmentation of the substantia nigra and some loss of pigment in the locus coeruleus. Microscopic examination revealed Lewy bodies in the substantia nigra, locus coeruleus and nucleus basalis. A few neurofibrillary tangles were also found in each H and E section. The locus coeruleus contained a mean of 5 Lewy bodies and 9.5 tangles in one side of each section. There was severe cell loss in the substantia nigra (7% of the number found in normal controls). The ventral tegmental area and locus coeruleus were also severely damaged. Cell loss in the nucleus basalis was severe, with 5 neurofibrillary tangles per section in addition to Lewy bodies. Large striatal neurons were sparse and the putamen contained some eosinophilic and argyrophilic axonal swellings. There were no Lewy bodies in the striatum, but a few intraneuronal neurofibrillary tangles were present, mainly in the caudate nucleus. No abnormalities were seen in the spinal cord.

In the cerebral cortex Lewy bodies were almost as numerous as in Case 1. However there were also large numbers of neurofibrillary tangles spread through all areas, but tending to spare the frontal lobes (fig. 1). Granulovacuolar degeneration affected 23% of hippocampal pyramidal cells, where they often coexisted with neurofibrillary tangles. Granulovacuolar degeneration was also present in the parahippocampal gyrus and temporal lobe. There were no Hirano bodies, Pick bodies or senile plaques.



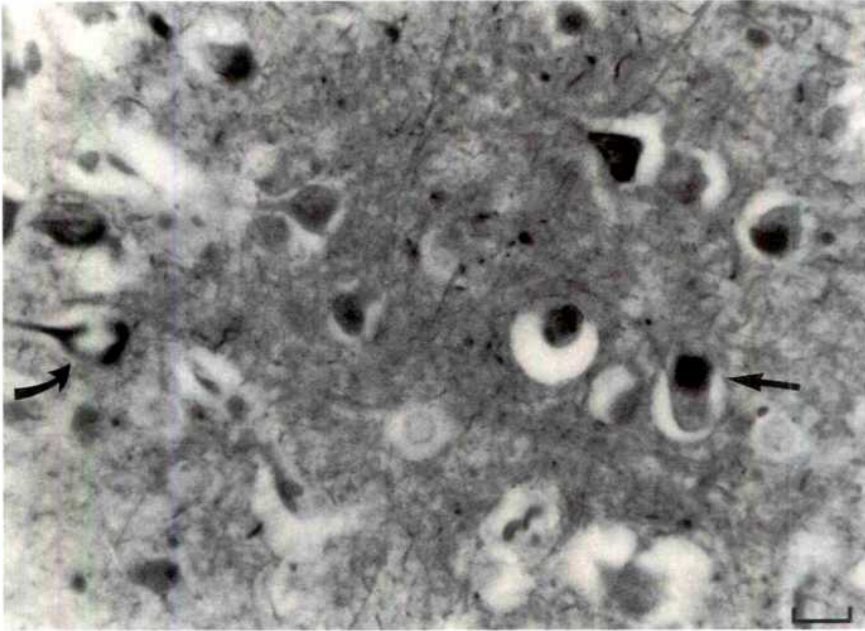


FIG. 1. Temporal lobe cortex in *Case 2* showing Lewy bodies in fifth cortical lamina (straight arrow) and tangles lying more superficially (curved arrow). Bielschowsky. Bar = 15  $\mu$ m.

### *Case 3*

At autopsy (Table 2) the body was wasted and bronchopneumonia was present. The brain showed moderate generalized enlargement of sulci and mild symmetric dilatation of the lateral ventricles. There was significant depigmentation of the substantia nigra. Histology showed cell loss and Lewy bodies in the substantia nigra, locus coeruleus and nucleus basalis. In the substantia nigra the cell loss was moderate and less severe than in most cases of Parkinson's disease (45% of the number found in normal controls). The paranigral nucleus and central linear nucleus were severely involved, but a few degenerate cells remained in the paranigral nucleus. There was moderate cell depletion in the locus coeruleus and nucleus basalis, but the striatum appeared normal.

In the cerebral cortex Lewy bodies were mainly found in the temporal lobe. In contrast, senile plaques were widespread with highest counts in the temporal and parietal lobes. Plaques of all sizes were scattered through the cortical layers, the larger coalescing together. Plaques were plentiful in the hippocampus and spread to the area striata. In some areas they were more numerous in sulci, but plaque amyloid was infrequent. Granulovacuolar degeneration involved 2% of hippocampal pyramidal cells and a few neurofibrillary tangles were also restricted to the hippocampus.

*Case 4*

At autopsy (Table 2) generalized body wasting and bronchopneumonia were present. The right suprarenal gland weighed 12 g and contained a cortical adenoma 2 cm in diameter. There was slight generalized atrophy of the brain and mild dilatation of the lateral ventricles. Microscopic examination found Lewy body degeneration in the substantia nigra, locus coeruleus and nucleus basalis. Cell loss in the substantia nigra, which was similar to the Lewy body-Parkinson's disease control group was 25% of the mean normal control value, and the ventral tegmental area was similarly affected. The nucleus basalis was moderately involved.

Lewy bodies were found in the temporal, frontal and parietal lobes but were less numerous than in other cases. Numerous senile neuritic plaques were found in all cerebral lobes, but were fewer in the occipital lobe and striate area. Neurofibrillary tangles were infrequent, and granulovacuolar degeneration and Hirano bodies were not found.

*Lewy body distribution in the cerebral cortex (Table 3)*

Lewy bodies in cortical cells were most numerous in the temporal, parietal and frontal lobes and less frequent or absent in the occipital lobe, particularly the striate area. There were few Lewy bodies in the subiculum and none in the hippocampus. Counts of Lewy bodies were variable, and pale bodies were not counted in areas where Lewy bodies were few or absent. In some locations both Lewy bodies and pale bodies were absent. Counts of Lewy bodies in Cases 1 and 2 found them to be sparse in the subiculum, tending to become more frequent in the parasubiculum and parahippocampal gyrus. Lewy bodies were identified in small and medium-

TABLE 3. LEWY BODY, NEUROFIBRILLARY TANGLE AND SENILE PLAQUE COUNTS IN AREAS OF THE CEREBRAL CORTEX\*

| <i>Case</i> | <i>Parahippocampus</i> | <i>Temporal lobe</i>                         | <i>Frontal lobe</i>               | <i>Parietal lobe</i>             | <i>Occipital lobe</i>             |
|-------------|------------------------|----------------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|
| 1           | Lb 10                  | Lb 8.9<br>(4-19)                             | Lb 11.2<br>(0-28)                 | Lb 12.3<br>(0-24)                | Lb 7.7<br>(3-15)                  |
| 2           | Lb 5                   | Lb 5.8<br>(3-8)<br>Tangles 5.0<br>(0-10)     | Lb 9.2<br>(6-15)<br>0.66<br>(0-2) | Lb 9.0<br>(0-19)<br>4.1<br>(0-7) | Lb 4.0<br>(2-15)<br>0.89<br>(0-2) |
| 3           | Lb 5                   | Lb 3.1<br>(1-6)<br>Plaques 26.1<br>(SD 10.9) | +<br>20.1<br>(SD 8.5)             | +<br>30.8<br>(SD 11.2)           | —<br>18.5<br>(SD 11.9)            |
| 4           | Lb 2                   | Lb 0.25<br>(0-1)<br>Plaques 22.6<br>(SD 9.7) | +<br>20.0<br>(SD 11.3)            | +<br>24.6<br>(SD 11.2)           | —<br>7.6<br>(SD 5.4)              |

\*Lewy body counts represent mean (and range) from 6-10 locations in each cortical lobe and 1 location in the parahippocampus. Tangle counts report the mean (and range) from 20 locations in each lobe. Plaque counts report the mean (and SD) from 10 locations. Lb = Lewy body. + = present. — = absent.

sized pyramidal neurons of the fifth and sixth cortical laminae. In Case 2 they were occasionally found in layer 3. The distribution of pale bodies was similar to that of Lewy bodies.

*Distribution of Alzheimer change in Cases 2, 3 and 4 (Table 3)*

In Case 2 tangles were present in every field and their regional localization did not correspond exactly to that of Lewy bodies. Tangles but not Lewy bodies were found in the hippocampus whereas tangles were less frequent in frontal and occipital lobes, where Lewy bodies were numerous. In Cases 3 and 4 the hippocampus and occipital lobe contained numerous plaques but no Lewy bodies.

*Lewy body morphology in the cerebral cortex (Table 4)*

Cortical Lewy bodies were less easily seen than those in the brainstem (fig. 2). They were smaller and more variable in shape, varying from round to triangular or irregular. The less intense staining often gave poor demarcation between the body and halo. Some appeared as though they were compressed beside the nucleus. Their staining reactions were similar to brainstem Lewy bodies. They were PAS negative and argyrophilic. Bielschowsky and Palmgren silver impregnations showed staining at the centre of the Lewy bodies, which is also the site of maximum staining with H and E and other stains (fig. 3). Many brainstem Lewy bodies also showed concentrations of silver staining at their periphery. Pale bodies, which were most numerous in Case 1, did not show central eosinophilia or other staining affinity (fig. 4). Bodies that were otherwise typical of Lewy bodies, but found lying free in the neuropil, were only rarely seen. Ultrastructural study showed that filaments of cortical Lewy bodies were randomly arranged but aggregated towards the centre (fig. 5). The haphazard pattern of filaments contrasts with the structure of classical

TABLE 4. MORPHOLOGICAL CHARACTERISTICS OF CORTICAL AND BRAINSTEM LEWY BODIES AND PALE BODIES

|                  | <i>Cortical Lewy bodies</i>         | <i>Brainstem Lewy bodies</i>                                                              | <i>Pale bodies</i>                                            |
|------------------|-------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Light microscopy |                                     |                                                                                           |                                                               |
| Size             | 5-15 $\mu$ m                        | 5-25 $\mu$ m                                                                              | 5-30 $\mu$ m in brainstem;<br>3-10 $\mu$ m in cerebral cortex |
| Shape            | Oval, 3-sided, rounded              | Round, elongated                                                                          | Variable, smooth edge                                         |
| Halo             | Present                             | Present                                                                                   | Absent                                                        |
| Body             | Less staining, no laminations       | Eosinophilic laminations                                                                  | No staining, no laminations                                   |
| Core             | Absent                              | Present                                                                                   | None                                                          |
| Number           | Usually single                      | Often multiple                                                                            | Single                                                        |
| Ultrastructure   |                                     |                                                                                           |                                                               |
| Core             | No core                             | Granular core, with dense circular outlines of filaments                                  |                                                               |
| Body             | Randomly orientated, loosely packed | Radially orientated, linear outlines, laminations due to variations in density of packing |                                                               |

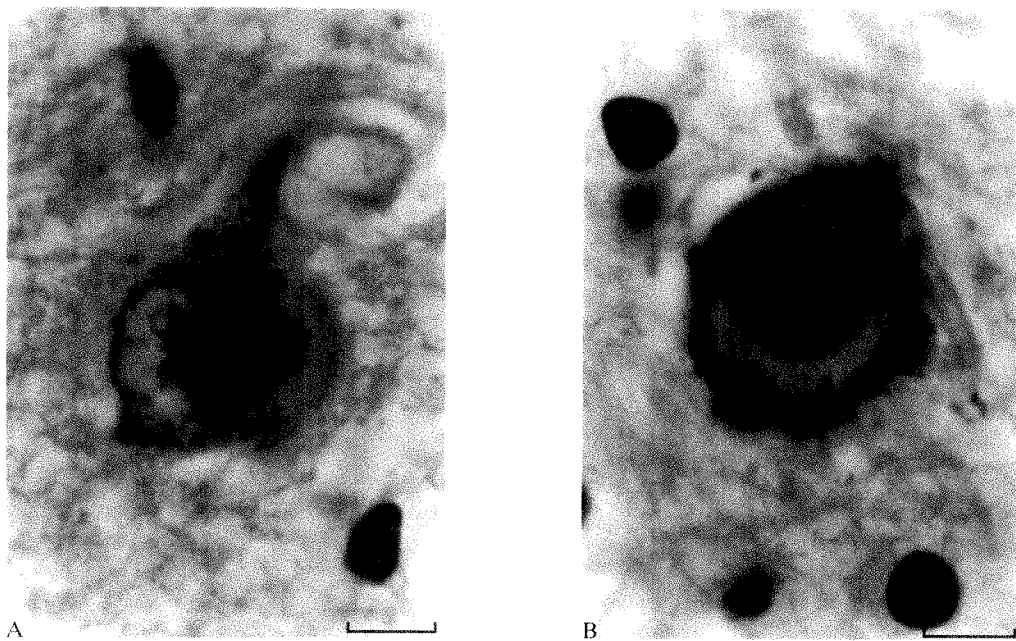


FIG. 2. A, cortical Lewy body. Haematoxylin and eosin. B, Lewy body in the substantia nigra with surrounding melanin granules. Haematoxylin and eosin. Bars =  $10\mu\text{m}$ .

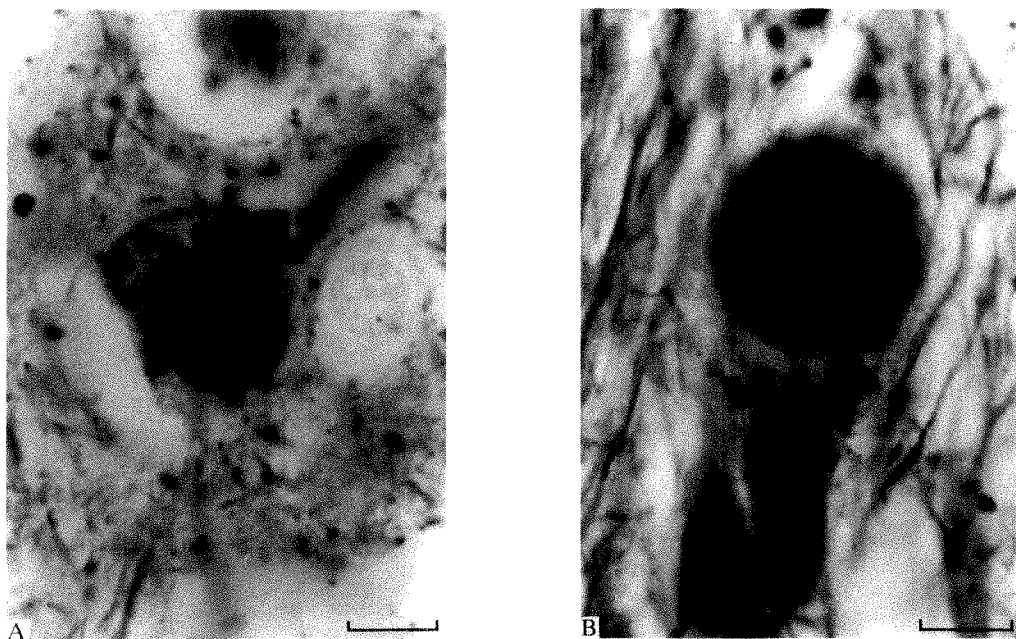


FIG. 3. A, cortical Lewy body with central staining. Bielschowsky. B, Lewy body in locus coeruleus showing central staining, one lamination of staining and a strongly staining halo. Bielschowsky. Bars =  $10\mu\text{m}$ .



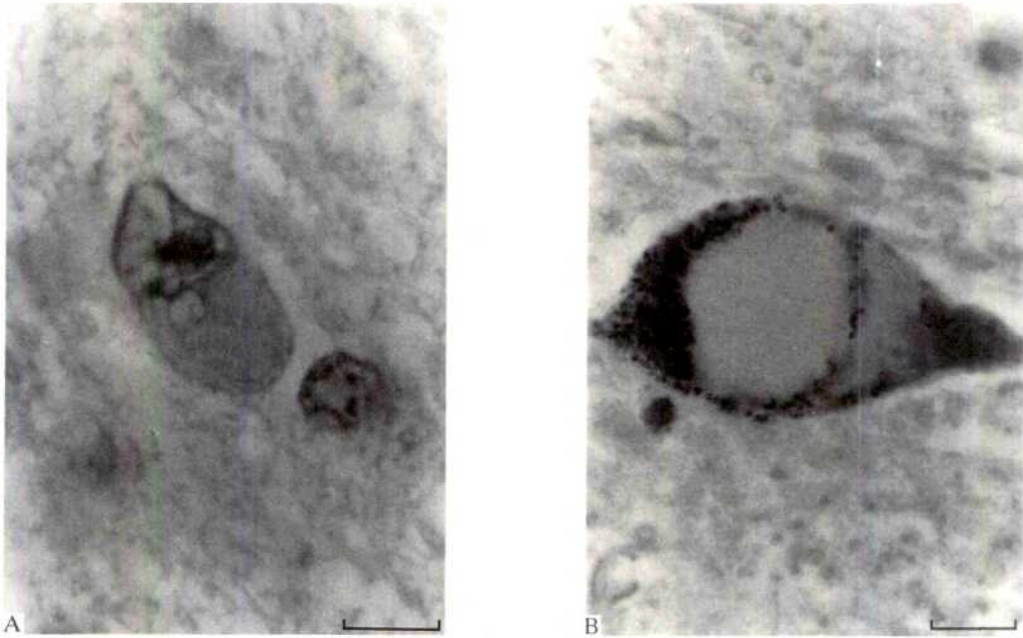


FIG. 4. A, cortical pale body. There is no staining of the inclusion. Haematoxylin and eosin. B, pale body in the substantia nigra with a finely granular texture and no staining. Haematoxylin and eosin. Bars = 10  $\mu$ m.

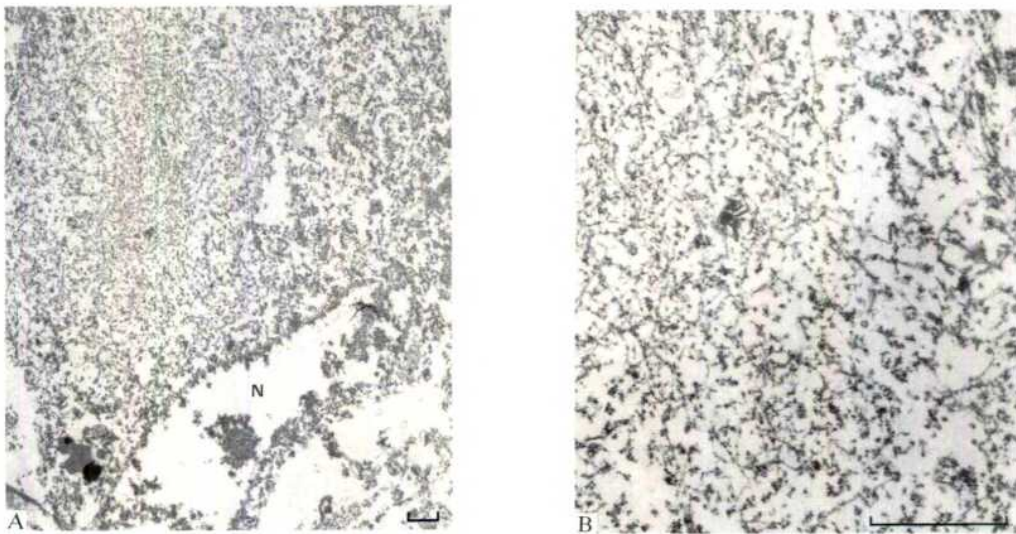


FIG. 5. A, ultrastructure of cortical Lewy body showing its filamentous composition. N = nucleus. B, the diameter of the Lewy body filaments is approximately 11 nm. Bars = 1  $\mu$ m.

Lewy bodies in the brainstem, which have central cores often of a granular consistency and peripheral radially orientated filaments.

## DISCUSSION

### *Clinical features*

All patients had severe dementia, a parkinsonian syndrome and cortical and brainstem Lewy body pathology. Severe Alzheimer's disease type dementia does not usually develop early in the course of brainstem Lewy body-Parkinson's disease. In Cases 3 and 4 dementia preceded the parkinsonian syndrome by up to 18 months, but in Case 2 the first indication of neuropsychological impairment appeared 3 yrs after the onset of extrapyramidal signs.

Okazaki *et al.* (1961) reported 2 cases with progressive dementia, followed within 14 months by immobility and rigidity of the limbs, and death at the ages of 68 and 70 yrs. Lewy bodies were found 'at various levels of the nervous system' including the substantia nigra, locus coeruleus and hypothalamus. In all areas of the cerebral cortex numerous Lewy bodies were located in medium-sized neurons. There were no obvious sites of predilection and all layers, except the first cortical layer, were involved. Senile plaques were sparse although they were more numerous in one case, and neurofibrillary tangles were not reported. A total of 23 similar cases (15 male, 8 female) have been reported in the Japanese literature under the rubric of dementia with cortical Lewy bodies (Table 5). Their mean age at onset was 56.7 yrs (range 26–72 yrs), with 3 cases younger than 40 yrs. Most of the reports give scanty clinical findings. Dementia was often a presenting feature and became an important characteristic in all but one case in which bradykinesia appeared at the age of 30 yrs (Ikeda *et al.*, 1975, 1978; Yoshimura *et al.*, 1977; Kosaka *et al.*, 1984). As in our Cases 2 and 4, confusional states, paranoid delusions and visual and auditory hallucinations were reported. In Case 1 the presence of dysphasia suggested temporal lobe damage. Topographical amnesia is believed to be a feature of parietal lobe damage and occurred in Case 3. In the patient described by Mitsuyama *et al.* (1984) this symptom was also described, but the other published reports do not record signs specifically indicative of cortical damage. Minagawa *et al.* (1980) mentioned bradyphrenia, which is often interpreted as suggestive of caudate nucleus pathology or damage to the ascending dopaminergic mesolimbic pathway. In our Case 3 the parkinsonian syndrome was mild and in 4 of the reported Japanese cases no parkinsonian syndrome was recorded at all (Kosaka, 1978; Kosaka *et al.*, 1978a, 1980, 1984; Kuroda *et al.*, 1978; Yagishita *et al.*, 1980; Ikeda *et al.*, 1980). Three of our cases had rest tremor but a description of limb tremor was recorded in only 9 of the 23 cases in the literature. Case 2 received L-DOPA and an initial response was seen although complications of therapy emerged within 4 months. L-DOPA was described as remarkably effective in the case of Ikeda *et al.* (1975, 1978), but in 2 other cases its effect was transient and negligible (Yoshimura *et al.*, 1980; Kosaka *et al.* 1984; Mitsuyama *et al.*, 1984). In the 4 cases

TABLE 5. CORTICAL LEWY BODY DISEASE: CLINICAL FEATURES OF REPORTED CASES

|                                                                                                  | <i>Age at onset<br/>(yrs)</i> | <i>Sex</i> | <i>Duration of<br/>disease (yrs)</i> | <i>First symptom(s) and sign(s)</i>                                          | <i>Other features</i>                                             |
|--------------------------------------------------------------------------------------------------|-------------------------------|------------|--------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1. Okazaki and Lipkin (1961)                                                                     | 67                            | M          | 14 mo.                               | Weight loss, disorientation, hallucinations                                  | 'Rigidity in flexion'                                             |
| 2. Okazaki and Lipkin (1961)                                                                     | 70                            | M          | Not stated                           | Disorientation, incontinence                                                 | Emaciation, dysarthria, limb flexion                              |
| 3. Kosaka <i>et al.</i> (1973)                                                                   | 47                            | F          | 8                                    | Dementia, rigidity, finger tremor, bradykinesia                              |                                                                   |
| 4. Ikeda <i>et al.</i> (1975, 1978); Yoshimura <i>et al.</i> (1977); Kosaka <i>et al.</i> (1984) | 30                            | M          | 8                                    | Rigidity, stooped posture, pulsion, slight tremor                            | L-DOPA effective, ?mental deterioration                           |
| 5. Kono <i>et al.</i> (1976)                                                                     | 55                            | F          | 13                                   | Dizziness, hand tremor, bradykinesia                                         | Dementia, rigidity                                                |
| 6. Kosaka (1978), Kosaka <i>et al.</i> (1976, 1978a, 1980, 1984)                                 | 56                            | F          | 9                                    | Involuntary movements, dementia, tremor, rigidity                            | Forgetful at 56 yrs                                               |
| 7. Kosaka (1978), Kosaka <i>et al.</i> (1978a, 1980, 1984)                                       | 57                            | M          | 5                                    | Dementia                                                                     | Limb flexion, akinetic mutism                                     |
| 8. Kosaka (1978), Kosaka <i>et al.</i> (1978a,b, 1980, 1984)                                     | 67                            | M          | 3                                    | Depressed, paranoid                                                          | Dementia, rigidity, tremor                                        |
| 9. Kuroda <i>et al.</i> (1978)                                                                   | 55                            | F          | 6                                    | Memory impairment                                                            | Progressive                                                       |
| 10. Ogasawara <i>et al.</i> (1978); Monma <i>et al.</i> (1979, 1981)                             | 62                            | F          | 7                                    | Dementia                                                                     | Tremor and rigidity                                               |
| 11. Kosaka and Mehraen (1979), Kosaka <i>et al.</i> (1984)                                       | 70                            | F          | 2                                    | Dementia                                                                     | Rigidity, tremor                                                  |
| 12. Kosaka and Mehraein (1979), Kosaka <i>et al.</i> (1984); Yoshimura (1982, 1983)              | 53                            | M          | 12                                   | Psychosis at 45 yrs                                                          | Rigidity, bradykinesia at 53 yrs, dementia                        |
| 13. Yagishita <i>et al.</i> (1980)                                                               | 55                            | F          | 10                                   | Dementia, disorientation                                                     | Progressive                                                       |
| 14. Yoshimura <i>et al.</i> (1980); Kosaka <i>et al.</i> (1984)                                  | 60                            | M          | 15                                   | Postural dizziness at 60 yrs, hypotension at 68 yrs, L-DOPA transient effect | Bradykinesia, rigidity at 69 yrs, marked dementia by 70 yrs       |
| 15. Okeda <i>et al.</i> (1982)                                                                   | 26                            | M          | 24                                   | Paranoia at 26 yrs                                                           | Dementia at 37 yrs, parkinsonian syndrome at 41 yrs               |
| 16. Yoshimura (1982, 1983); Kosaka <i>et al.</i> (1984)                                          | 58                            | M          | 12                                   | Dementia, rigidity, aphasia                                                  |                                                                   |
| 17. Yoshimura (1982, 1983); Kosaka <i>et al.</i> (1984)                                          | 59                            | F          | 6                                    | Dementia, severe muscle rigidity, slight hand tremor                         |                                                                   |
| 18. Yoshimura (1982, 1983); Kosaka <i>et al.</i> (1984)                                          | 63                            | M          | 4                                    | Dementia, severe limb rigidity, slight hand tremor                           | Chorea                                                            |
| 19. Yoshimura (1982, 1983); Kosaka <i>et al.</i> (1984)                                          | 72                            | M          | 4                                    | Dementia, rigidity, paranoia                                                 |                                                                   |
| 20. Ikeda <i>et al.</i> (1980); Kosaka <i>et al.</i> (1984)                                      | 66                            | M          | 3                                    | Dementia                                                                     | Rigidity and tremor, bedridden                                    |
| 21. Kayano <i>et al.</i> (1980)                                                                  | 38                            | M          | 12                                   | Psychosis                                                                    | Dementia, rigidity                                                |
| 22. Minagawa <i>et al.</i> (1980)                                                                | 56                            | M          | 4                                    | Bradypnea                                                                    | Dementia, rigidity                                                |
| 23. Mitsuyama <i>et al.</i> (1984)                                                               | 64                            | M          | 4                                    | Dementia, topographical disorientation                                       | Stooped gait 2 yrs after onset, L-DOPA 1.5 g daily no improvement |

reported here the progression of the illness was more rapid than is generally seen in Parkinson's disease and in the late stages of disease immobility and severe dementia were present. In 22 of the reported cases, the mean duration was 7.8 yrs, which is considerably shorter than the mean life expectancy recorded in most

studies of Parkinson's disease. Severe muscle rigidity and an advanced stage of dementia were commonly recorded before death.

### *Pathological features*

Neuropathological examination showed that the brain of Case 4 was low in weight. The mean brain weight in the 18 cases in the literature was 1206.8 g (1075–1440 g) and focal or generalized cortical cerebral atrophy was reported in 4 (Table 6). In our cases the pathology in subcortical regions was identical to that found in Parkinson's disease. However, in Case 2 subcortical neurofibrillary tangles were also present. In Case 3 nigral cell loss was only mild. This finding was also reported in the 2 cases of Okazaki *et al.* (1961) and in that of Yagishita *et al.* (1980), whose patient did not have a parkinsonian syndrome. It was not possible to relate changes at any subcortical site to the cortical pathology, for example the ventral tegmental area was not completely destroyed in Case 3 and the nucleus basalis of Meynert was mildly affected in Case 1.

In our 4 patients Lewy bodies were located in the fifth and sixth cortical layers, with a few in the third cortical layer of Case 2. In 4 published cases they were also present in the third layer and in the 2 cases of Okazaki *et al.* (1961) in all but the first cortical layer. In the reported cases Lewy bodies were spread through all cerebral lobes, with a predilection for temporal, anterior frontal, insular cortex and anterior cingulate gyrus. Among our cases the most marked cortical Lewy body pathology was found in Case 1. In this patient there was additional pathology in the nuclei gracilis and cuneatus and there were axonal swellings in the occipital lobe, all of which are features of Hallervorden-Spatz disease. Of particular note was the complete absence of neocortical tangles or plaques, which is also true for reported cases of Hallervorden-Spatz disease with cortical Lewy bodies. In this case the tendency for overlap in terms of Lewy body pathology is interesting, but the absence of degeneration or iron deposition in the globus pallidus makes a diagnosis of Hallervorden-Spatz disease untenable. In Cases 2, 3 and 4 the severity of tangle or plaque disease was sufficient for a second diagnosis of Alzheimer's disease to be made (Blessed *et al.*, 1968; Wilcock and Esiri, 1982), but their regional distribution did not consistently correlate with that of the Lewy body pathology. Here Lewy body pathology appears to be the principal disease process on the basis that Alzheimer's disease is not usually associated with cortical Lewy bodies. Cortical Lewy bodies never occur in any number in the absence of brainstem Lewy bodies. Other authors have rated the severity of senile plaque and neurofibrillary tangle disease as mild, moderate or severe, and in 12 of the 23 published cases there was severe plaque or tangle disease, possibly of a severity compatible with Alzheimer's disease. In 8 cases there were many plaques, in 1 case there were many tangles and in 3 cases, both plaques and tangles. Three others had moderate numbers of plaques. In 1 case there were no Alzheimer changes (Ikeda *et al.*, 1975, 1978) and in the remaining 10 cases only mild changes were reported. The ultrastructure of Lewy bodies in Case 1 showed loosely and randomly orientated



TABLE 6. CORTICAL LEWY BODY DISEASE: PATHOLOGICAL FEATURES OF REPORTED CASES

| Case no.* | Brain wt (g) | Lewy bodies in cortical layers | Tangles              | Plaques | Other features                                                                |
|-----------|--------------|--------------------------------|----------------------|---------|-------------------------------------------------------------------------------|
| 1         | 1098         | —                              | —                    | +       |                                                                               |
| 2         | 1342         | All but 1                      | —                    | (+)     |                                                                               |
| 3         | —            | —                              | +++                  | —       |                                                                               |
| 4         | 1320         | 5, 6 occasionally 3            | 0                    | 0       |                                                                               |
| 5         | 1175         | —                              | 0                    | +++     | Lewy bodies in sympathetic ganglia                                            |
| 6         | 1130         | 5, 6                           | +++ esp. hippocampus | +++     | Localized atrophy of hippocampus, Hirano bodies, granulovacuoles, Pick bodies |
| 7         | 1200         | 5, 6                           | ++ esp. hippocampus  | +++     | Hirano bodies, gvd, ?Pick bodies                                              |
| 8         | —            | 5, 6                           | + only hippocampus   | ++      | Hirano bodies, gvd, ?Pick bodies                                              |
| 9         | 1100         | 5, 6                           | +                    | +       |                                                                               |
| 10        | 1000         | —                              | +                    | +       | Localized temporal lobe atrophy, Pick bodies                                  |
| 11        | 1120         | 5, 6 rarely 2, 3               | +                    | ++/+++  | Hirano bodies, gvd                                                            |
| 12        | 1340         | 5, 6                           | +                    | +/++    | Hirano bodies, gvd                                                            |
| 13        | 1075         | 5, 6 rarely 3                  | +++                  | +++     | Hirano bodies, gvd                                                            |
| 14        | —            | —                              | ++                   | +++     |                                                                               |
| 15        | —            | 5, 6                           | + only hippocampus   | 0       |                                                                               |
| 16        | —            | 5, 6                           |                      |         |                                                                               |
| 17        | 1150         | 5, 6                           | +                    | +++     | Hirano bodies, gvd                                                            |
| 18        | 1140 (1440)  | 5, 6                           | +                    | +++     |                                                                               |
| 19        | 1250         | —                              | +                    | ++      |                                                                               |
| 20        | 1292         | —                              | +++                  | +++     |                                                                               |
| 21        | 1250         | —                              | +                    | 0       |                                                                               |
| 22        | 1440         | —                              | +                    | ++      |                                                                               |
| 23        | 1300         | 5, 6                           | + only hippocampus   | +++     | Slight atrophy                                                                |

\*Case nos as in Table 5. (+) sparse, + few, ++ moderate, +++ severe, 0 none, — not reported, gvd = granulovacuolar degeneration.

filamentous components of approximately 11 nm in diameter. The centres of the Lewy bodies were composed of more closely packed filaments. This structure is unlike the granular centre and radial orientation of filaments seen in classical brainstem Lewy bodies (Duffy and Tennyson, 1965). Other authors describe filaments ranging from 5 to 20 nm in diameter (Ikeda *et al.*, 1975; Kosaka, 1978; Yoshimura, 1982, 1983). Degenerating mitochondria and other organelles are also seen among the filaments. Immunocytochemical study of cortical Lewy bodies was first reported by Goldman *et al.* (1983), who used four different polyclonal rabbit antisera directed against neurofilament polypeptides. They stated that cortical Lewy bodies displayed homogeneous staining and that some showed accentuation of staining at the periphery. Nakazato *et al.* (1984) also prepared polyclonal antisera to each of the three human neurofilament proteins and obtained immunostaining in the centre of some cortical Lewy bodies similar to the pattern observed with brainstem Lewy bodies.

It is reasonable to conclude from our data and this review that the presence of widespread cortical Lewy bodies may or may not be linked with excessive plaques or tangles, or both, and that Alzheimer changes, if present, do not show strict regional correlation with Lewy bodies.

### *Diagnosis of parkinsonian syndrome with dementia*

The prevalence of dementia in established idiopathic Parkinson's disease is not known, but a figure of 20% has been suggested (Brown and Marsden, 1984). Dementia occurring early in Parkinson's disease or preceding its onset is rare. The characteristic frontolimbic form of dementia in Parkinson's disease is dominated by bradyphrenia, with slowing of thought processes, difficulty switching mental sets, loss of initiative, apathy and depression. Loss of short-term memory combined with aphasia, apraxia, agnosia and spatial disorientation is characteristic of dementia associated with pathological changes in the temporoparietal cortex. This is less often seen in Parkinson's disease and may be no commoner than in an age-matched elderly population (Lees, 1985). In Cases 1 and 3 the clinical features suggest temporoparietal damage. The combination of a parkinsonian syndrome and dementia is seen in a number of disorders (Table 7). The commonest temporoparietal dementia is Alzheimer's disease in which some clinical studies have found a high prevalence of bradykinesia and rigidity. Pearce (1974) noted mild bradykinesia and muscular rigidity in 61% of 65 patients and Drachman and Stahl (1975) observed axial rigidity, retropulsion and a positive glabellar tap in 5 of 9

TABLE 7. MAIN CAUSES OF DEMENTIA AND PARKINSONIAN SYNDROME

| <i>Disorder</i>                                                  | <i>Distinguishing clinical and pathological features</i>                                                                                                                                          |
|------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alzheimer's disease                                              | Temporoparietal symptoms, multiple plaques or tangles in neocortex, without Lewy bodies                                                                                                           |
| Progressive supranuclear palsy                                   | Fronto-limbic symptoms, cervical dystonia, supranuclear gaze palsy, pseudobulbar palsy, characteristic signs may be delayed (Pfaffenbach <i>et al.</i> , 1972), tangles in brainstem with gliosis |
| Hallervorden-Spatz disease                                       | Onset usually in 1st or 2nd decades, dystonia, pyramidal signs, cerebellar signs, degeneration and pigmentation of the globus pallidus                                                            |
| Corticobasal degeneration                                        | Involuntary movements, cortical sensory loss, pyramidal signs, pale inclusions in central sulcus and parietal lobe and substantia nigra, but no Lewy bodies                                       |
| Vascular dementia                                                | Multiple strokes, stepwise progression, pseudobulbar palsy, hypertension, infarcts on CT, periventricular lucencies                                                                               |
| Communicating hydrocephalus                                      | Severe postural instability, urinary incontinence, CT shows distension of ventricles without cortical atrophy                                                                                     |
| Progressive subcortical glial dystrophy (Neumann and Cohn, 1967) | Extensive cortical and subcortical gliosis                                                                                                                                                        |
| Pick's disease variants                                          | Frontal or temporal lobar atrophy, Pick bodies in Ammon's horn                                                                                                                                    |
| Parkinsonism-dementia of Guam                                    | Neurofibrillary tangles in brainstem and cerebral cortex                                                                                                                                          |
| Sporadic motor neuron disease (Hudson, 1981)                     | Invariable association with motor neuron disease, tangles in brainstem, loss of anterior horn cells                                                                                               |

patients. In 3 of the 5 patients L-DOPA improved motor function. However, a classical rest tremor is found less often and has been reported in 4% of 71 patients (Sulkava, 1982) and 10% of 143 patients (Mölsä *et al.*, 1984). These studies lack pathological diagnoses and the proportion with Lewy bodies and cell loss in the substantia nigra is unknown. Furthermore the parkinsonian features are usually mild and occur only in the terminal phase. Pick's disease may rarely show extra-pyramidal features as part of the clinical picture. Akelaitis (1944) described such a patient with a variant of Pick's disease manifesting dementia, parkinsonian syndrome and cortical and subcortical pathology. Atrophy and cell loss in subcortical sites were greatest in the caudate nucleus and less marked in the globus pallidus, subthalamic nucleus and substantia nigra. Pick's disease is characterized pathologically by frontal or temporal lobar atrophy. The presence of Pick bodies may cause confusion with cortical pale bodies or with cortical Lewy bodies. Unlike pale bodies and Lewy bodies, Pick bodies are often found in hippocampal pyramidal and granule cells and when present in the neocortex are located in the second and third cortical layers with fewer in the sixth layer. Pick bodies tend to be well circumscribed, basophilic and stain well with silver, whereas pale bodies do not react with silver and Lewy bodies show less intense reactions. Pale-staining inclusions can also be found in the substantia nigra in Pick's disease. Pick bodies were not found in our cases. It is probable that in 4 of the reported cases (Table 6) the possibility of Pick bodies was suggested by the presence of cortical pale bodies. At the ultrastructural level Pick bodies contain apparently normal filaments (Wiśniewski *et al.*, 1972), but a variety of other filament inclusions are described, including straight filaments (Munoz-Garcia and Ludwin, 1984) and paired helical filaments (Schochet *et al.*, 1968). Their structural arrangement is unlike that in the Lewy body.

Morris *et al.* (1984) described 10 members of one family, similar to a family reported by Kim *et al.* (1981), in which the main features were a temporoparietal dementia, parkinsonian syndrome and autosomal dominant inheritance. Pathological examination in 4 cases showed Pick-type lobar atrophy, some senile plaques and spongiform degeneration of the outer layers of the cerebral cortex, associated with loss of large and small neurons. However, ill-defined cytoplasmic inclusions containing 'argyrophilic fibrillary material' were reported and in one case Lewy bodies were found in the substantia nigra.

In corticodentatonigral degeneration with neuronal achromasia (corticobasal degeneration) the mild parkinsonian features include slowness of movement and unsteady gait, and in 2 of 3 original cases some mental deterioration occurred late in the disease (Rebeiz *et al.*, 1968). Dementia was also present in 4 of 6 other suspected cases, only one of which was examined pathologically (Watts *et al.*, 1985). These reports also record unusual choreiform involuntary movements, limb apraxia, cortical sensory impairment and extensor plantar responses. The achromatic cortical inclusions described in this disorder resemble the pale body. However, they are larger, more clearly defined and are mostly seen around the

central sulcus and in the parietal lobe. In the substantia nigra some are indistinguishable by light microscopy from pale bodies.

### *Hallervorden-Spatz disease*

Hallervorden-Spatz disease is the one other condition in which multiple Lewy bodies have been described in the cerebral cortex. It is a slowly progressive motor disorder usually starting in the first two decades of life and characterized by dystonia, muscular rigidity, pyramidal signs and dementia (Dooling *et al.*, 1974). However, Jankovic *et al.* (1985) recently reported a 68-yr-old man with late onset Hallervorden-Spatz disease presenting with a parkinsonian syndrome. Three years later he had dementia, severe blepharospasm, apraxia of eyelid opening, aphonia and immobility, terminating in death 13 yrs from the onset. Iron deposition and axonal spheroids were present in a number of areas, particularly in the globus pallidus, but there were no Lewy bodies.

The diagnostic hallmark of Hallervorden-Spatz disease is degeneration of the pallidonigral system with focal axonal swellings and dark ferruginous discolouration. There may also be a more widespread neuroaxonal dystrophic process, variably present at cortical, subcortical, brainstem and medullary levels, when the distinction from infantile neuroaxonal dystrophy becomes blurred. Ultrastructurally the axonal swellings contain granular material, mitochondria, vesicular profiles and occasional filaments. Eleven of 80 pathologically reported cases have been associated with Lewy bodies in the substantia nigra, and at other locations such as the locus coeruleus and nucleus basalis (Dooling *et al.*, 1974; Kalyanasundaram *et al.*, 1980; Williamson *et al.*, 1982). In 4 of these cases (Helfand, 1935; Defendini *et al.*, 1973; Dooling *et al.*, 1974; Williamson *et al.*, 1982) Lewy bodies have been reported in the cerebral cortex as well as in the brainstem. Neurofibrillary tangles are described in Hallervorden-Spatz disease (Wisniewski *et al.*, 1979), but both plaques and tangles were absent in the 4 cases with cortical Lewy bodies.

### *Classification of cortical Lewy body disease*

The classification of cortical Lewy body disease has been uncertain, but Okeda *et al.* (1982) criticized the view that it was a separate entity from Lewy body-Parkinson's disease. The variation in severity of reported cases and the occurrence of isolated Lewy bodies in the temporal lobes of Parkinson's disease suggest a spectrum of disease. Three cases with an intermediate syndrome with mental deterioration, parkinsonian syndrome and small numbers of Lewy bodies restricted to the temporal lobe were reported by Forno (1969) and Forno *et al.* (1978). Yoshimura (1982, 1983) separated 55 cases of Parkinson's disease into 3 groups depending on an approximate assessment of mental state and of the severity of cortical Lewy body disease. Four cases (Yoshimura, 1982, 1983; Table 5) had dementia, muscle rigidity and scattered cortical Lewy bodies. Moderate or severe senile plaque involvement was also present in all cerebral lobes with accentuation

in the occipital lobes. There were a few tangles in the temporal lobe. In a second group of 15 cases, 7 were believed to show slight to severe dementia. As a whole they had fewer cortical Lewy bodies and less Alzheimer-type pathology. In the 36 remaining cases without dementia, Lewy bodies were believed to be even less numerous in the diencephalon and brainstem, and cerebral Lewy bodies were not found. The frequency of 'senile changes' corresponded to age alone. In view of the relationship between Lewy bodies and plaques this suggested that plaques might be responsible for the dementia. Prospective evaluations of dementia severity and accurate quantitative histology, however, were not done. More recently Kosaka *et al.* (1984) postulated that Lewy bodies were responsible for dementia. This view is supported by our Case 1 and the cases of Okazaki *et al.* (1961) and Kayano *et al.* (1980) in which Alzheimer-type changes were mild. The case of Ikeda *et al.* (1975, 1978; Table 5) appears to contradict this as Lewy bodies were found in the cortex without Alzheimer changes or obvious dementia, but detailed neuropsychological assessment was not performed (Kosaka *et al.*, 1984). Furthermore, in the 4 cases of Hallervorden-Spatz disease (reviewed above), cortical Lewy bodies were numerous and dementia was severe, but Alzheimer change was absent.

There is insufficient evidence to link the cortical and subcortical Lewy body pathology. Mild disease in the nucleus basalis in Case 1 is inconsistent with an important role for this subcortical area in the production of the dementia. It is likely that the ventral tegmental area is affected secondarily.

Recent clinical and pathological evidence has questioned whether the prevalence of Alzheimer's disease in Parkinson's disease is greater than that of a chance association (Nakano and Hirano, 1984; Lees, 1985), although our recent personal observations and those of Tomlinson and Corsellis (1984) suggest the possibility of some link between senile plaques and brainstem Lewy body disease (similar to Cases 3 and 4). However, in diffuse cortical Lewy body disease, which is part of the Lewy body-Parkinson's disease spectrum, there appears to be some association with Alzheimer disease pathology. Our observations and an estimate of published cases suggest that half have pathology similar or identical to Alzheimer's disease. In cortical Lewy body disease the Lewy bodies seem to be responsible for dementia, with the effects of Alzheimer disease pathology being a variable addition. Cortical Lewy body disease should be considered in any patient with a temporoparietal dementia and idiopathic Parkinson's disease. To date the term diffuse Lewy body disease has been suggested for cases of cortical Lewy body disease or those with autonomic failure (Kono *et al.*, 1976; Yoshimura *et al.*, 1980). In keeping with the terms idiopathic brainstem Lewy body disease or Lewy body-Parkinson's disease, we prefer that the association of dementia and idiopathic Parkinson's disease with brainstem Lewy bodies and multiple cortical Lewy bodies be called idiopathic diffuse cortical Lewy body disease or Lewy body dementia.

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## POSTERIOR CALLOSAL INFARCTION

### CLINICOPATHOLOGICAL CORRELATIONS

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#### SUMMARY

Clinicoanatomical observations on a patient with partial interhemispheric disconnection associated with complete ischaemic destruction of the splenium and of the posterior part of the body of the corpus callosum are presented. Neuropathological examination of the areas containing degenerated white matter indicated that the lesions affected the transcallosal fibres that link the cortex of the occipital lobes and the superior parietal lobules (SPL). The white matter situated in the temporal lobes was intact. This suggests that in man, and contrary to what has been described in the monkey, the callosal pathway followed by the temporal fibres is rostral to the one followed by the parietal or at least by the SPL fibres.

The most prominent disconnection syndrome elements were left tactile anomia (in spite of a rather good tactile-motor integration between the hemispheres), left visual anomia, agraphia of the left hand and 'diagnostic' apraxia. The fact that the anterior part of the corpus callosum was intact accounts for the preservation of interhemispheric transfer of somatic sensory information and for the absence of left extinction during the dichotic listening test. An attempt is made to give a more detailed explanation of the results obtained during the different tests.

#### INTRODUCTION

The best documented syndromes of interhemispheric disconnection are in patients subjected to commissurotomy for the treatment of severe epilepsy (Sperry *et al.*, 1969; Gazzaniga, 1970) or for the surgical exploration of the third ventricular region (Trescher and Ford, 1937; Maspes, 1948; Gazzaniga and Freedman, 1973; Iwata *et al.*, 1974; Jeeves *et al.*, 1979; Damasio *et al.*, 1980). When the postoperative syndromes in these cases are considered, it is often difficult to determine the exact contribution from extracallosal damage as opposed to that from the commissurotomy itself. To the best of our knowledge no case of an interhemispheric disconnection syndrome associated with an anatomically verified lesion confined to the corpus callosum of an otherwise healthy human brain has been reported. Our present observation approaches this ideal. The interhemispheric disconnection syndrome was partial and related to a lesion that was clearly limited to the posterior corpus callosum; consequently, we were able to correlate anatomical and clinical

findings. Furthermore, since the lesion was old, the location and the resulting white matter degeneration provided data concerning the callosal connections of the human cortex. Previous publications pertaining to the clinical study of this case include a prediction of the anatomical lesions (Barbizet *et al.*, 1974) and a complementary study of visual performance (Lhermitte *et al.*, 1976).

### CASE REPORT

S. was a right-handed 75-year-old woman. On February 26, 1971, while driving her car she suddenly experienced a severe headache and blurred vision. She managed to return home but during the days following this incident her family and doctor noticed that her gait and memory were impaired. However, she did not enter hospital until one month later. At this time neurological examination revealed an alert patient with reduced spontaneous movement of the right arm and leg. Although no segmental motor weakness was disclosed she was unable to walk unsupported without immediately falling towards her right. Fine finger movements were normal. The plantar reflexes were both flexor. Hypalgesia and defective position sense were detected on the right side of her body. On the left, the only problem was the misnaming of objects that she palpated with her left hand. Her vision was restricted to the central zone. When an object was presented to her, eye fixation was obtained only by chance and visual pursuit was impossible. S. could move her eyes correctly to the right and to the left whenever she was requested to do so; however, she was unable to raise them above the horizontal. Her handwriting was poor with micrographia. No language disorder was disclosed and, in particular, the patient continued to be able to name colours. There was no evidence of acalculia, difficulty in distinguishing right from left, asomatognosia, anosognosia, or of visual neglect. The motor deficiency interfered with the assessment of right-sided apraxic disorders that later became evident. On the left, although objects were put to correct use, at times symbolic or mimed gestures seemed to be disturbed by a searching movement of her hand. There was no orofacial apraxia. The patient was unable to retain questions that she had been asked 5 min earlier, nor could she describe the various homes in which she had lived over the years or arrange in chronological order facts that she had been able to recall. She was noticeably disorientated in time and space but showed no tendency for erroneous recognition. She stated that the onset of her illness coincided with the disappearance of dream activity. The EEG carried out on March 23, 1971, was normal; on April 16 bilateral occipital slow monomorphic delta waves were observed on an irregular background. Between May 7–10, 1971, the patient's condition deteriorated rapidly. Drowsiness and incontinence appeared and the motor and somatosensory deficit affecting her right arm and leg became accentuated. A loss of gaze movement and an inability to recognize objects and people were also noted, although the patient remained able to recognize a few colours. The EEG showed polymorphic delta slow wave activity over the posterior part of the left hemisphere. One month later a CT 99 m brain scan revealed an area of early uptake in the left temporo-occipital zone and an area of delayed uptake in the right parieto-occipital zone.

From June 1971, the patient's state of consciousness, gait and vision improved progressively until her condition stabilized itself in October, 1971. Slight problems with gait and fine finger movements, as well as brisk tendon reflexes and impaired position sense persisted on the right. On the left, only somatosensory extinction existed. Strikingly, although she palpated objects with her left hand in a rapid and precise manner, she named and described them incorrectly (tactile anomia). Gaze movements were normal; optokinetic nystagmus was elicited in all directions. Goldman perimetry showed a bilateral reduction of the peripheral visual field; macular vision, part of the right inferior quadrant and most of the left visual field were spared. Visual acuity was 6/10 for both eyes. The patient's oral language capacities, her memory and her ability to execute transitive and intransitive gestures were intact. She showed no attention deficit; in fact she was very cooperative and persevering during the tasks. In December 1973 a repeat CT 99 brain scan disclosed no abnormal uptake.

From 1974 until 1979, S. lived in a home for the aged and, during this time, no further neurological disorder appeared. Her diminished vision was partially accounted for by glaucoma in her right eye. Left tactile anomia was observed each time it was sought. In September 1979, S. died of septicaemia.

## STUDY OF INTERHEMISPHERIC EXCHANGE OF SENSORY AND MOTOR INFORMATION

### *Clinical observations*

We personally examined S. on a regular basis from March 1972 to November 1973. Throughout this entire period a partial interhemispheric disconnection syndrome was consistently observed.

S. was able to name and to describe objects that were hidden out of sight behind a screen if she was permitted to feel them with her right hand. Left hand palpation was less successful in that she almost always misnamed the object: the name chosen often corresponded to an object that had been presented to her earlier or to one that had been recently mentioned. When she was asked to describe an object held in her left hand, S. was either incapable of doing so or else she described the object whose name she had just incorrectly given.

When the patient held an object in each of her hands she invariably claimed that her left hand was empty and sometimes she made large searching movements with her left arm. However, this did not prevent her from manipulating the object spontaneously in a correct manner. For example, she would rub the bristles of a toothbrush and open and close a clothes peg or a pair of spectacles even though she verbally disclaimed any awareness of the presence of these objects in her left hand.

When she was asked to use the object that she was holding in her left hand, S. usually did so in a way that was adapted to the name she had just given it, whether this name was correct or not. However, at times correct usage was observed in spite of incorrect naming. For example, even though she mistook a pair of spectacles for a pair of scissors she put them on correctly; she called a spoon a needle but she brought it to her mouth as if feeding herself; she decided to give the name 'lighter' to a hairbrush but, although she mimed the action of lighting a cigarette with her right hand, she brushed her hair with her left hand; she was incapable of naming a thimble but placed it on her finger correctly.

When she was blindfolded the patient had no difficulty in naming areas of the right side of her head and body that the examiner touched. When the situation was reversed to examine areas of the left side of her head (i.e., her hair, eyebrow, forehead, nose, upper lip, cheek, ear and chin), 20 attempts at verbal identification led to only two errors: 'the side of my nose' when her upper lip was touched and 'my eyebrow' when her forehead was touched. Both of these errors were subsequently corrected. These results contrast with those obtained through stimulation of the left side of her body as opposed to her face: she could name none of the regions that were being stimulated, although she could use either hand to

## Left hand

Dictation: 'Je suis venue à l'hôpital'  
(I came to hospital)

Dictation of letters

O U B B G S S

Reproduction of letters

Model B S Copy B S

## Right hand

Dictation

Spontaneous writing

FIG. 1. Left hand agraphia.

indicate them. When the examiner touched two fingers of one of her hands she could use the opposite hand's thumb to indicate the two fingers of that hand that corresponded to those being touched. Regardless of the arm chosen to carry out the task, S. usually had more success at reproducing a position that had previously been imposed on the same arm than at imitating a position that was actually being imposed on the opposite arm.

The patient could write correctly with her right hand but when she used her left hand the results were lacking in form (fig. 1). She could identify letters and numbers that were traced on the palm of her right hand but this was impossible when her left hand was stimulated in the same way. However, she could name simple letters

that she was made to draw through passive movements of either of her arms and, whether the movements used proximal or distal joints, the results were identically successful.

Tasks concerning the copying of figures with cubes and matches as tools were incorrectly performed by her right hand although some of the same figures were correctly copied by her left hand.

S. could use both sides of her body to execute meaningful gestures (symbolic or mimed gestures) and she could imitate gestures that were presented visually to her. However, when the examiner merely described these gestures orally (e.g., raise your arm in front of you, to the side, above your head; bend and straighten out your forearm; use your thumb and one other finger to form a circle) many errors were observed on the left side of her body. These errors were particularly frequent for hand and finger gestures, less frequent for the forearm and practically nonexistent when the movement called for the use of the proximal part of the arm. In September 1973, two years after the initial experiment, only finger movement errors persisted.

The patient was unable to describe postures that were imposed on her forearm, hand or fingers unless she was offered a choice between two simple alternatives such as 'up' or 'down'.

During a test that required the cross-matching of objects, S. said 'My hands don't agree with each other'. To explain the meaning of this remark she told the story of herself frying a steak, turning it over in the frying pan with her right hand and, immediately after, finding herself turning it over once again with her left hand. She also explained that she was often unaware of an object that she had in fact been holding in her left hand for several minutes: 'I can be holding a knife in my left hand while I cook but it is only when I cut myself with it that I am astonished to discover its presence'. Misadventures such as these made her fear for her sanity. The patient also declared that she often had to interrupt her activities before being able to resume and finish them successfully. However, even when blindfolded she could accomplish tasks, such as tying a knot, that required coordinated hand activity.

#### *Formal testing*

Two sets of 7 objects were used. (1) objects that were considered 'significant' (SO): a champagne cork, a clothes peg, a sea shell, a spoon, a ball-point pen and a key. (2) Objects of different geometrical shapes that were considered 'nonsignificant' (NSO).

The patient was given time to acquaint herself with the SOs so that, from the beginning, she was thoroughly familiar with the objects among which she would have to choose. Each test began either with visual presentation, tactile presentation or the naming of each of the 7 objects that belonged to one of the sets described above (input). The patient was then asked to name these objects or, in accordance with the multiple choice method, to point to or to retrieve 1 of the 7 objects (output). Success frequencies were calculated after 3 to 24 tests (21 to 169 trials). The tests are summarized below according to their respective modes of entry (input) and their numbering corresponds to output and to the numbering of the squares in Tables 1 and 2.

#### *Input: left hand palpation*

1: left-handed retrieval of the object just palpated by the same hand.

- 2: right-handed retrieval of the duplicate of the object just palpated by the left hand.
- 3: naming the object just palpated by the left hand.
- 4: pointing to the duplicate of the object just palpated by the left hand. The patient was usually asked to use her right hand since her left hand was slower and its use led to identical results.

*Input: right hand palpation*

- 5: left-handed retrieval of the duplicate of the object just palpated by the right hand.
- 6: right-handed retrieval of the object just palpated by the same hand.
- 7: naming of the object just palpated by the right hand.
- 8: pointing to the duplicate of the object just palpated by the right hand. For the same reason as in Test 4 the patient was asked to use her right hand.

*Input: the examiner naming an object*

- 9: left-handed retrieval of the named object.
- 10: right-handed retrieval of the named object.
- 11: pointing to the named object. Identical results were obtained whichever hand was used.

*Input: the sight of an object placed in free view*

- 12: left-handed retrieval of the duplicate of the object.
- 13: right-handed retrieval of the duplicate of the object.
- 14: naming the object.

Tests for visual processing were conducted by tachistoscropy in both fields (Prof. F. Lhermitte's Laboratory, Hôpital de la Salpêtrière, Paris). A photograph of an object or letter was flashed in the right or left visual field. The patient was then asked to name or to point to the object or letter whose image she had just seen. Success frequencies were obtained after 4 tests (24 trials). The number of each test described below indicates the corresponding square in Table 3.

15 and 16: naming the object or capital letter flashed in the left (Test 15) or the right (Test 16) visual field.

17 and 18: pointing to the duplicate of the photograph that had just been flashed in the left (Test 17) or in the right (Test 18) visual field. The duplicate was to be found among 6 photographs all of which were placed in free view.

A dichotic listening test using the material elaborated by Michel and Péronnet (1975) was performed in November 1973. Two different digits (between 1 and 13) were simultaneously presented, one to each ear, at equal sensation levels. The patient was asked to repeat all digits heard. Twenty pairs of digits were presented in this manner. The same experiment was performed with 10 pairs of monosyllabic and 30 pairs of disyllabic words. The patient had previously shown herself to be able to repeat items correctly when only one ear was stimulated at a time.

*Statistical methods.* For each test the binomial distribution was used to calculate the probability of a significant difference between success frequency and success frequency due to chance. When the results of two tests were compared a fourfold  $\chi^2$  test permitted the assessment of the statistical difference between success frequencies. A partition of  $\chi^2$  was used when the results of more than two tests were compared (Fleiss, 1981). When we wished to study, for example, the influence of input (left or right hand) and output (ipsilateral or contralateral) on SO or NSO retrieval, a factorial testing design was used and, in this case, the influence of each separate factor and the influence of their interactions was determined by analysis of variance after angular (arc sine) transformation (Snedecor and Cochran, 1980).

*Results.* The ratios of correct responses to the number of trials can be summarized as follows. The results obtained during tests 1–14 are presented in Tables 1 and 2; those for tests 15–18 are given in Table 3. These results mainly show a left tactile and visual anomia. However, the left tactile anomia, in contrast to the left visual anomia, is not complete; the proportion of correct responses, although low, is different from chance (0.256 vs 0.143,  $P < 0.001$ ). Left-handed retrieval of an object

named by the examiner led to better results (0.612 vs 0.256,  $P < 0.001$ ). A certain amount of interhemispheric exchange for stereognosis is maintained, with better results for NSO than for SO. When the retrieval was changed from ipsilateral to

TABLE 1. FREQUENCIES OF SUCCESS ACCORDING TO DIFFERENT INPUT/OUTPUT COMBINATIONS FOR SIGNIFICANT OBJECTS (SO) OR NONSIGNIFICANT OBJECTS (NSO)

| Input  |    | LH                | RH               | D                | S               |                                           |
|--------|----|-------------------|------------------|------------------|-----------------|-------------------------------------------|
| Output |    |                   |                  |                  |                 |                                           |
| SO     | 1  | 5                 | 9                | 12               |                 |                                           |
|        | LH | 0.810<br>(51/63)  | 0.571<br>(48/84) | 0.612<br>(49/84) | 0.333<br>(7/21) | LH 1↔2,3,4 $P < 0.001$<br>3↔4 $P < 0.001$ |
|        | 2  | 6                 | 10               |                  |                 |                                           |
|        | RH | 0.371<br>(39/105) | 1.000<br>(63/63) | 1.000<br>(21/21) |                 | RH 5↔6,7,8 $P < 0.001$                    |
| NSO    | 3  | 7                 | 14               |                  |                 |                                           |
|        | D  | 0.256<br>(43/168) | 1.000<br>(21/21) | 1.000<br>(21/21) |                 |                                           |
|        | 4  | 8                 | 11               |                  |                 |                                           |
|        | S  | 0.512<br>(86/168) | 1.000<br>(21/21) | 1.000<br>(21/21) |                 |                                           |
| NSO    | 1  | 5                 | 12               |                  |                 |                                           |
|        | LH | 0.786<br>(66/84)  | 0.726<br>(61/84) | 0.810<br>(51/63) |                 | LH 1↔2 $P < 0.001$<br>4↔(1,2) $P < 0.05$  |
|        | 2  | 6                 | 13               |                  |                 |                                           |
|        | RH | 0.405<br>(34/84)  | 0.905<br>(57/63) | 1.000<br>(21/21) |                 | RH 5↔(6,8) $P < 0.05$                     |
| NSO    | 4  | 8                 |                  |                  |                 |                                           |
|        | S  | 0.600<br>(63/105) | 1.000<br>(21/21) |                  |                 |                                           |

LH=left hand; RH=right hand; D=denomination; S=sight. The test numbers are used to indicate all the significant paired comparisons between the results for both the LH and the RH inputs, respectively; furthermore the score obtained by the denomination of a SO palpated by the LH (3) is different from chance level ( $1/7 = 0.143$ ,  $P < 0.001$ ) and from the score of the left-handed retrieval of a named object (3↔9,  $P < 0.001$ ).

TABLE 2. INTERACTION BETWEEN IPSILATERAL OR CONTRALATERAL RETRIEVAL (FACTOR A) ACCORDING TO THE SIGNIFICANCE OR NONSIGNIFICANCE OF THE OBJECTS (FACTOR B) AND THE SIDE OF THE ENTRY (FACTOR C)

| Output | Ipsilateral retrieval |         | Contralateral retrieval |         |
|--------|-----------------------|---------|-------------------------|---------|
| Input  | LH                    | RH      | LH                      | RH      |
| SO     | 1 0.810               | 6 1.000 | 2 0.371                 | 5 0.571 |
| NSO    | 0.786                 | 0.905   | 0.405                   | 0.726   |

LH=left hand; RH=right hand; SO=significant object; NSO=nonsignificant object. Frequencies of success presented in Table 1 are redistributed using such a factorial design to demonstrate (1) a significant factor C contribution, i.e., better results with the right hand entry than with the left hand entry ( $P < 0.001$ ), and (2) a significant A-B interaction, i.e. a fall in success rate significantly smaller for NSO than for SO when retrieval was changed from the ipsilateral to the contralateral ( $P < 0.05$ ).



contralateral, the fall in the NSO results was significantly less than that for the SO results (Table 2).

The dichotic listening test results given in Table 4 show no left ear extinction.

TABLE 3. LEFT VISUAL ANOMIA\*

| Output<br>Input | Pointing |       | Denomination |       |
|-----------------|----------|-------|--------------|-------|
|                 | LVF      | RVF   | LVF          | RVF   |
| SO              | 0.833    | 1.000 | 0.167        | 1.000 |
| L               | 0.750    | 1.000 | 0.000        | 1.000 |

\* There is a significant interaction ( $P < 0.001$ ) between the retrieval method (pointing or naming) and the side of entry, i.e., the fall in success rate was significantly smaller for pointing than for denomination when input was moved from the right visual field to the left. LVF = left visual field entry; RVF = right visual field entry; SO = significant object; NSO = nonsignificant object.

TABLE 4. NUMBER OF CORRECT (+) OR INCORRECT (−) REPETITIONS OF PAIRS OF DIGITS OR WORDS. NO LEFT EAR EXTINCTION

|             | Left ear + | Left ear − | Total |
|-------------|------------|------------|-------|
| Digits      |            |            |       |
| Right ear + | 7          | 8          | 15    |
| Right ear − | 11         | 4          | 15    |
| Total       | 18         | 12         | 30    |
| Words       |            |            |       |
| Right ear + | 3          | 12         | 15    |
| Right ear − | 17         | 8          | 25    |
| Total       | 20         | 20         | 40    |

## NEUROPATHOLOGICAL EXAMINATION

### Methods

After horizontal section of the mesencephalon, the brain was cut in coronal slices. The cerebellum and unseparated brainstem were cut in horizontal slices. Nine verticofrontal bihemispheric brain slices and 6 horizontal slices of the mesencephalon, pons and medulla oblongata were embedded in celloidin; the blocks of the posterior hemisphere were cut semiserially. The sections were stained with haematoxylin and eosin, and with the Loyez stain for myelin. Small specimens of the posterior corpus callosum and parieto-occipital white matter were embedded in paraffin and stained with haematoxylin and eosin, Massons trichrome and by Bodian silver impregnation combined with Luxol fast blue.

### Results

Four types of change were observed.

1. The lateral ventricles, the foramen of Monro and the third ventricle were dilated (figs 2, 3, 6). The aqueduct was slightly dilated. The volume of the fourth ventricle was normal. The cerebral cortex was macroscopically normal, with no evidence of atrophy or of infarcts.

2. The splenium and the posterior part of the body of the corpus callosum were

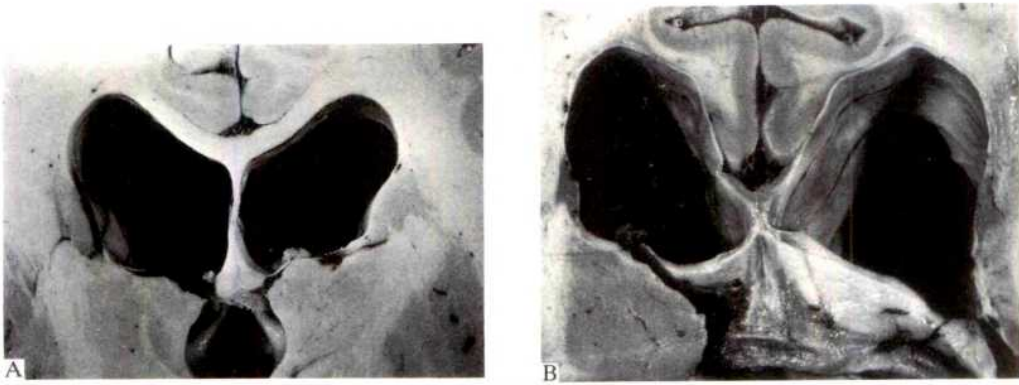


FIG. 2. A, coronal section of the cerebral hemispheres through the mamillothalamic tracts showing normal corpus callosum and ventricular dilatation. B, coronal section of the cerebral hemispheres through the pulvinar; the shrunken splenium is viewed from behind. The lateral ventricles are dilated.

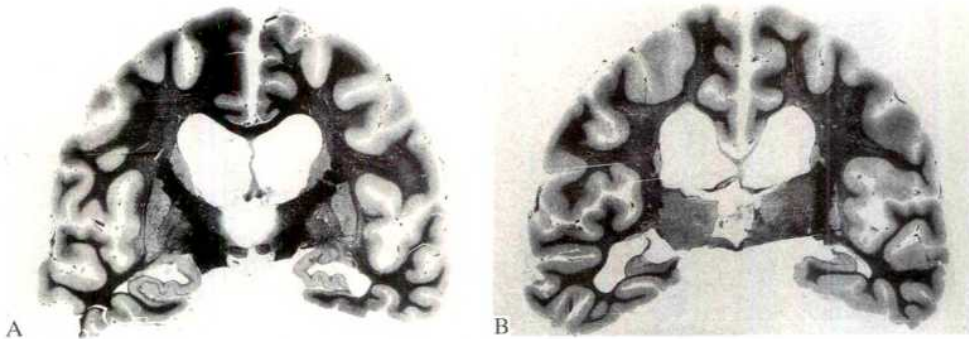


FIG. 3. A, coronal section of the cerebral hemispheres through the mamillary bodies showing dilatation of the lateral and third ventricles, and normal corpus callosum, frontal and temporal white matter, and cortex. B, coronal section of the cerebral hemispheres through the posterior part of the thalamus showing ventricular dilatation and necrosis of the corpus callosum. Loyez stain.

the site of old necrotic lesions (figs 2B, 3B, 4). This type of lesion also existed bilaterally in the white matter surrounding the occipital horn of the lateral ventricles at the level of the calcarine sulcus (fig. 6C, D). All these regions appeared to be atrophic. They all showed extensive degeneration involving axons and myelin, and also astrocytic gliosis with areas of complete cavitating parenchymatous disintegration. Macrophages were rare. No inflammatory infiltrates were observed.

3. Bilaterally symmetric degenerative lesions involved the white matter of the superior parietal lobules and occipital gyri. They consisted in incomplete patchy myelin loss with astrocytic gliosis; axons were reduced in number. The U fibres were spared (fig. 6). Slight neuronal loss was found in the third layer of the corresponding cortical regions. The distribution of these lesions (fig. 5) led us to consider them as resulting from the degeneration of the callosal forceps major radiations secondary to the necrosis of the posterior part of the corpus callosum.

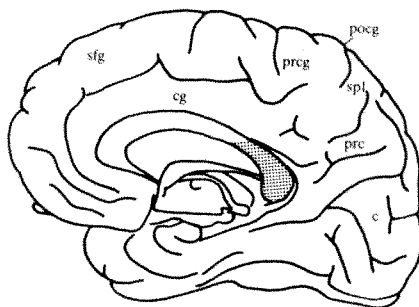


FIG. 4. Topography of the necrosis of the corpus callosum. sfg = superior frontal gyrus; cg = cingular gyrus; prcg = precentral gyrus; pocg = postcentral gyrus; spl = superior parietal lobule; prc = precuneus; c = cuneus.

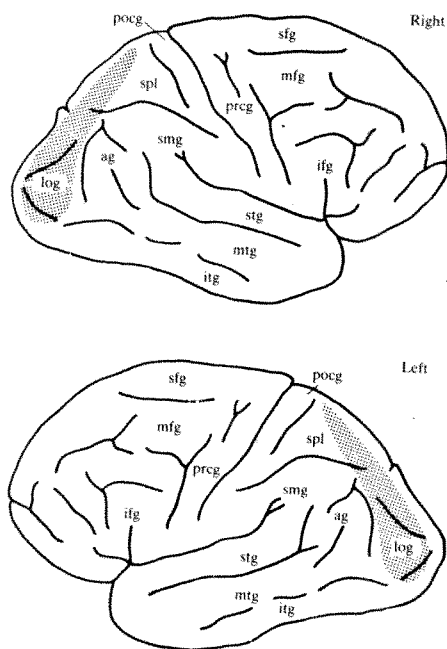


FIG. 5. Topography of the degeneration of the parieto-occipital white matter. sfg = superior frontal gyrus; mfg = middle frontal gyrus; ifg = inferior frontal gyrus; prcg = precentral gyrus; pocg = postcentral gyrus; spl = superior parietal lobule; smg = supramarginal gyrus; ag = angular gyrus; log = lateral occipital gyri; stg = superior temporal gyrus; mtg = middle temporal gyrus; itg = inferior temporal gyrus.

4. The basilar artery, the supraclinoid carotid arteries, the circle of Willis, the anterior, middle and posterior cerebral arteries and all of the meningocortical arteries were examined. These extracerebral vessels were all histologically normal; they showed no atherosclerosis and no occlusion. Hyalinization of the walls of small arteries and arterioles was often noted when sections of intraparenchymatous blood vessels were examined. Moreover, many perivascular spaces were distended

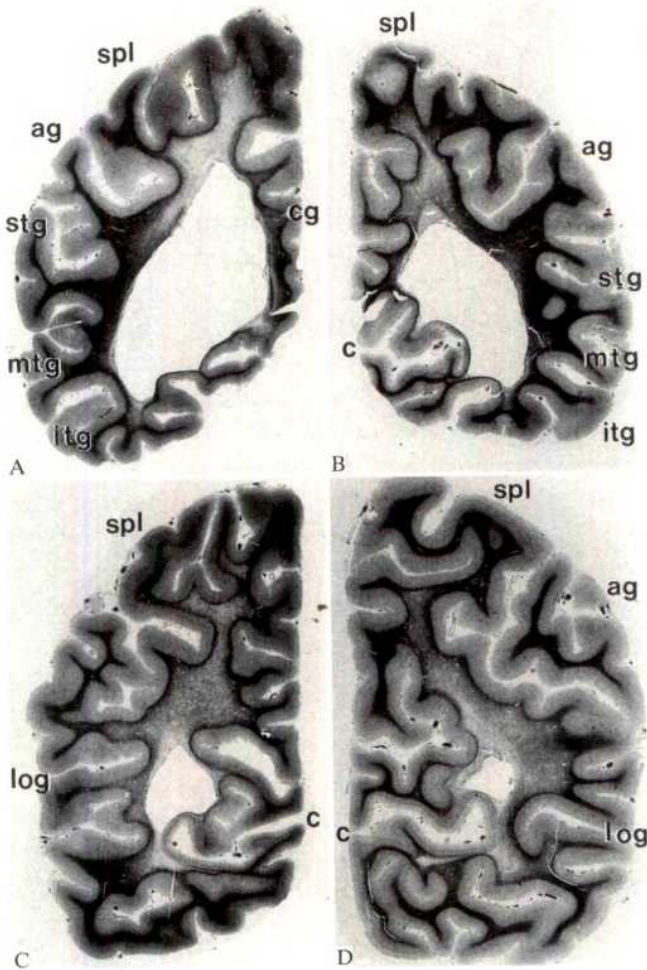


FIG. 6. Coronal sections of the cerebral hemispheres (A, C: left; B, D: right) through the posterior part of the temporal lobes (A, B) and posterior horn of the lateral ventricles (C, D) showing ventricular dilatation, necrosis of the white matter surrounding the occipital horn of the lateral ventricle involving the optic radiations, and degeneration of the white matter of the superior parietal lobules and occipital gyri sparing the U fibres. Loyez stain. spl = superior parietal lobule; ag = angular gyrus; stg = superior temporal gyrus; mtg = middle temporal gyrus; itg = inferior temporal gyrus; log = lateral occipital gyri; c = cuneus; cg = cingular gyrus.

and some of these contained a few macrophages. These lesions were particularly numerous in the lentiform nucleus (especially on the right) as well as in the thalamus and in the white matter of both cerebral hemispheres. A lacune (small deep infarct) was observed in the posterior region of the right putamen. The vessel walls in the globus pallidus were mineralized, especially in the right hemisphere.

5. Except for rather numerous grey matter heterotopias within the right frontal and parietal white matter, the other cerebral structures were macroscopically and microscopically normal. In particular this was true for the rostrum and the anterior region of the body of the corpus callosum (figs 2A, 3A, 4). It was also true of the

fimbriae, the fornix, the hippocampal commissure, the anterior commissure, the mamillary bodies, the cerebellum, the brainstem, the temporal isthmus and the cerebral cortex, including the hippocampus.

## DISCUSSION

The clinical study of this case permitted an accurate prediction of the neuropathological findings (Barbizet *et al.*, 1974). The diagnosis of infarction of the vertebrobasilar territory, which seemed clinically probable, was confirmed by the finding of necrotic lesions in the occipital regions and in the posterior part of the corpus callosum which are in the territory the posterior cerebral arteries (Foix and Masson, 1923; Stephens and Stilwell, 1969). These lesions are in accordance with the final clinical data (bilateral hemianopia and signs of callosal disconnection). Several points are of particular interest: the posterior part of the corpus callosum was totally destroyed so that no nervous structures remained in this area; the limits of this destruction were neatly circumscribed; the original lesion was several years old and therefore the subsequent degeneration allowed us to define the cortical zones involved in the disconnection; the other commissures were intact; and there were no cortical lesions.

All the white matter lesions, except for those situated around the occipital horns of the lateral ventricles had the typical characteristics of degeneration secondary to an interruption of the callosal fibres: they were symmetric, they spared the U fibres (fig. 6) and there was neuronal loss in the corresponding cortical regions. This degeneration was confined to the occipital and to the superior parietal lobule white matter (figs 5,6). The fact that the temporal lobes were unaffected is noteworthy. In view of these observations it seems possible to conclude that, in the human brain, the temporal lobe fibres follow a rostral pathway as compared with that followed by fibres from the parietal lobe, or at least with the pathway taken by the superior parietal lobule fibres. This pattern differs from that described in the most recent anatomical study concerning the cortical termination of callosal fibres in the Rhesus monkey (Pandya *et al.*, 1971) which showed that within the corpus callosum the parietal lobe fibres remain rostral to those from the temporal lobe. Results as different as these illustrate the risks incurred when animal data are extrapolated to the human brain, even when the data are obtained from primates. Recently de Lacoste *et al.* (1985) correlated the distribution of wallerian degeneration in the corpus callosum with the anatomical sites of focal lesions in man. Their results and ours agree with each other in that they are both in favour of a splenium pathway for fibres arriving from the superior parietal lobules as opposed to a more anterior pathway for those originating in the temporal lobes.

Our patient shared a certain number of clinical characteristics with patients having undergone forebrain commissurotomy (Sperry *et al.*, 1969; Gazzaniga, 1970): left-sided tactile (Table 1) and visual (Table 3) anomia, inability to name areas of the left side of her body (apart from facial areas) as they were being



touched by the examiner and agraphia with the left hand (fig. 1). However, contrary to split-brain patients (Sperry *et al.*, 1969), she continued to be able to indicate with the opposite thumb the two mirror fingers that corresponded to two fingers that were being touched on one side. This interhemispheric exchange of somesthetic information can be explained by the integrity of the part of the body of the corpus callosum which seems to be responsible for the transfer of intermanual information (Jeeves *et al.*, 1979; Bentin *et al.*, 1984). However, this transfer was insufficient for satisfactory cross-stereognostic recognition, since an object palpated by the right hand was less consistently retrieved by the left hand than by the right (Table 1, 5 vs 6,  $P < 0.001$  for SO and  $P < 0.05$  for NSO) and vice versa (Table 1, 2 vs 1,  $P < 0.001$ ). This somesthetic transfer was even less efficient for the naming of objects palpated by the left hand, since the score differs only slightly from chance (0.206 vs 0.143,  $P < 0.001$ ). It seems that we are in the presence of a gradient as far as the possibilities of interhemispheric transfer are concerned. Presumably the more the task calls for a posterior callosal transfer, the more the quality of the performance diminishes.

When our patient was blindfolded and asked to make a binary verbal choice ('up' or 'down') to describe a position held by a part of one of her left-sided limbs (fifth finger and hallux included), she was able to comply with ease. However, no description was possible when the position involved more than one joint or when no verbal alternative was offered. The results are identical to those observed in split-brain patients (Sperry *et al.*, 1969; McCloskey, 1973). As it has been described in the split-brain patients (Sperry *et al.*, 1969), our patient was able to reproduce positions that had been imposed on one of her limbs but was less successful at imitating positions that were being imposed on the opposite limb.

The maintained somesthetic interhemispheric exchanges could furnish a reasonable explanation for the immediate activation of left hemisphere language activity on arrival of somesthetic information originating in the right hemisphere, the end result of this being incorrect verbalization. Actually verbal activity was frequently observed even when it was specifically forbidden. According to our patient, silent verbalization followed palpation. She said that it was particularly frequent when she knew that the object belonged to the group of significant objects (SO) but that it also occurred, although to a lesser degree, with nonsignificant objects (NSO) that she had learned to identify during the course of the tests through a detail or the object's general shape. It was quite obvious that this silent verbalization created a disturbance that influenced the tests' results. To eliminate it as much as possible the observer placed himself in front of the patient, spoke to her and encouraged her to concentrate on the object's shape. However, this method was only partially and irregularly effective. The statistical study of the results confirms that incorrect verbalization did indeed play a disturbing role. When the patient was asked to search for an object that she had just palpated, whether this search was undertaken by the hand that had originally manipulated the object or not, left hand entry

proved to be less effective than right hand entry (Table 2,  $P < 0.001$ ); when retrieval was shifted from the ipsilateral to the contralateral side, the fall in the score associated with NSO retrieval was significantly less than that for SO retrieval (Table 2,  $P < 0.05$ ). Moreover, the success rates associated with SO identification after left hand palpation were 0.810 for left hand retrieval (Table 1, 1), 0.512 for visual identification (Table 1, 4), 0.371 for right hand retrieval (Table 1, 2) and 0.256 for naming (Table 1, 3). In view of these results it seems reasonable to presume that the disturbance created by incorrect verbalization was relatively small when the left hand was confronted with the task of searching for an object that it had just palpated; the disturbance should have been maximum when the right hand searched for an object palpated by the left hand and, in fact, the score is not significantly different from the one associated with the naming of an object palpated by the left hand. The score for visual identification after left hand palpation is intermediate, significantly lower than the one obtained through left hand retrieval ( $P < 0.001$ ) and higher than that for naming ( $P < 0.001$ ). This intermediate result probably depends on which occipital cortex commanded the pointing out of the object: the left occipital cortex, which was possibly disturbed by erroneous naming, or the right occipital cortex which had processed somaesthetic information at its disposal.

As it is the case with split-brain patients (Sperry *et al.*, 1969), S. was more successful at using her left hand to find an object that had been named by the examiner than she was at naming an object that she had palpated with her left hand (Table 1, 9: 0.612 vs Table 1, 3: 0.256,  $P < 0.001$ ). Whether the SOs were named (Table 1, 9) or palpated by the right hand (Table 1, 5) the scores associated with left hand retrieval were identical (0.612 and 0.517). This result is hardly surprising since immediate verbal identification always followed right hand palpation and, what is more, the patient then actually refused to continue to feel the object since, as she said 'It is useless to do so since I already know what all this is about'. Thus right hand palpation was almost equivalent to naming.

This right hemisphere comprehension capacity for oral language was also found for written language (Lhermitte *et al.*, 1976): when a short printed word was flashed in the left visual field our patient was able to indicate the corresponding picture or word written in cursive script.

It has been remarked that after forebrain commissurotomy, patients can no longer use their left hand and foot to reproduce positions that have just been described to them even though they continue to be able to imitate these positions (Sperry *et al.*, 1969). This was also true of our patient although, conversely, she remained capable of using her left arm to execute symbolic gestures and to mime the use of objects. In other words, there was no ideomotor apraxia of the left arm. One can surmise that these two types of gestures bring different callosal connections into play (Watson and Heilman, 1983). It is pertinent, however, to note that the former type of gesture, unlike the latter, is composed of several unrelated items and that the right hemisphere, although capable of grasping a simple order, seems

incapable of articulating more than two or three different verbal elements (Zaidel, 1978).

After forebrain commissurotomy, verbal description of movements that are to be carried out by the proximal part of the left arm prompt correct performance (Gazzaniga *et al.*, 1967). This was also true of our patient. It is in favour of an ipsilateral motor command for the proximal arm. This hypothesis is further supported by behaviour that we observed in our patient at several different times: when S. held an object in each of her hands she disclaimed any awareness of the object that she was in fact skilfully manipulating with her left hand and, at the same time, her left arm made large exploratory movements as if to search for this object. It is plausible to think that in this competitive situation, the amount of left side tactile information reaching the left (speaking) hemisphere was so small that this hemisphere made the patient express her unawareness of the object held in her left hand; in view of the fact that it was misinformed, the left hemisphere activated the left arm's ipsilateral driving system and, consequently, this arm was thrust out in search of the object; the right hemisphere, unaware of what was happening in the left hemisphere, simultaneously continued to exert efficient control over the left hand's palpation of the object thanks to the afferent information that it was receiving.

Left hand agraphia contrasting with an absence of ideomotor apraxia is a characteristic not only of our patient but also of other cases of partial lesions of the corpus callosum (Sugishita *et al.*, 1980; Gersh and Damasio, 1981).

'Diagnostic apraxia' has been described in patients who had undergone fore-brain commissurotomy (Van Wagenen and Herren, 1940; Akelaitis, 1945). It has occasionally been reported in other cases of commissurotomy (Zaidel and Sperry, 1977; Bogen, 1985) and in cases of spontaneous lesions of the corpus callosum (Barbizet *et al.*, 1978; Watson and Heilman, 1983). Approximately the same description is always given: each hand interferes with the other and, as in the 'frying pan' incident described by our patient, the left hand often undoes what the right hand has just accomplished. It is as if the right hemisphere was less concerned with motor intention of deliberate actions than the left (Barbizet *et al.*, 1978).

The dichotic listening test showed no left channel extinction (Table 4) although this is known to be one of the features of the interhemispheric disconnection syndrome (Milner *et al.*, 1968; Sparks and Geschwind, 1968; Springer and Gazzaniga, 1975). The word and digit material that we used could possibly explain these results (Springer *et al.*, 1978), although it seems pertinent to remark that this material succeeded in revealing a left ear extinction in other cases of inter-hemispheric disconnection (Michel and Péronnet, 1975; Barbizet *et al.*, 1978). Furthermore, the absence of left ear extinction is in accordance with the integrity of the anterior portion of the corpus callosum that seems to have a preponderant influence on the right-left transfer of dichotic information (Springer and Gazzaniga, 1975) and with the integrity of the temporal callosal fibres.



## ACKNOWLEDGMENTS

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# MOTOR CORTEX STIMULATION IN INTACT MAN

## 1. GENERAL CHARACTERISTICS OF EMG RESPONSES IN DIFFERENT MUSCLES

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### SUMMARY

This paper is the first of two papers describing our five-year experience with the technique of electrical stimulation of the human motor cortex. In this first paper we illustrate the basic distribution and behaviour of electromyographic responses in limb muscles to anodal stimulation of the motor cortex in intact, awake human subjects. These responses may be recorded at short latency, with estimates of conduction velocities from the brain to the spinal cord suggesting transmission in rapidly conducting pathways, such as the corticomotoneuronal component of the corticospinal tract. The site at which the stimulus activates these motor pathways to produce responses at such short latency is likely to be at, or adjacent to the origin of these major descending motor pathways in the cerebral cortex. The best stimulating sites for activation of arm or leg muscles corresponds to the known somatotopic arrangement of the cerebral cortex. The electromyographic response characteristics are different in the contracting, as compared with the relaxed muscle; the EMG response latency shortens, its size becomes larger and its threshold is lowered when the muscle is voluntarily made to contract.

The mechanisms that are responsible for these characteristics are examined in the following paper.

### INTRODUCTION

In 1980, Merton and Morton discovered that it was possible to stimulate the human brain through the intact scalp using single electric shocks delivered from a specially designed stimulator. They found that large transient voltages (of the order of 500 V) were required. The resistance between electrodes attached to the scalp proved to be highly nonlinear (*see Hill et al.*, 1980). With stimulus intensities of several hundred volts, the interelectrode resistance fell to very low values. Because of this, conventional stimulators, which may give adequate open-circuit voltages, are barely able to stimulate the brain, unless a special electrode montage is used (Rossini *et*

*al.*, 1985*b*). In general, a device with low output impedance is necessary so that a high voltage can be maintained across the skin.

Using such stimulators, the most easily excitable region of the human brain is the motor cortex. Stimulation over the central area of the scalp can produce a visible twitch of muscles on the contralateral side of the body at very short latency. There have been several reports showing that the technique can monitor function in central motor pathways (Cowan *et al.*, 1984; Dick *et al.*, 1984; Mills and Murray, 1985; Rossini *et al.*, 1985*a, b*; Snooks and Swash, 1985; Boyd *et al.*, 1986). In these papers we summarize our own five-year experience with brain stimulation. In the first paper we describe the general physiological characteristics of the evoked muscle responses in normal subjects. In the second (Day *et al.*, 1987), we concentrate on evidence suggesting that single anodal cortical stimulation in man produces multiple discharges of spinal motoneurons, perhaps by generating multiple descending volleys in fast corticomotoneuron pathways.

## METHODS

A total of 28 males and 2 females aged 20–58 years (mean 36,  $SD \pm 10$ ) have been examined during the course of these studies. All were experienced scientists, either working in the Neurology Department or visiting for short periods. Detailed and repeated investigations were performed on a smaller group of 6 individuals, including 4 of the authors (P.D.T., B.L.D., J.C.R., J.P.R.D). All subjects gave informed consent; the procedures had the approval of the local ethical committee.

The brain stimulator was made by Mr H. B. Morton, and is a prototype of the high-voltage stimulator available commercially (D180, Digitimer Ltd). It is capable of delivering stimuli of up to 600 V with a decay time constant of 50  $\mu$ s. Typical peak currents delivered at maximum intensity lie between 500 and 900 mA in different subjects. Throughout this and the subsequent paper, the intensity of the cortical stimulation is expressed as a percentage of the maximum output of the device. Bipolar stimulation was used in all the experiments described.

The anode and cathode were 9 mm diameter Ag/AgCl electrodes fixed to the scalp with collodion. Stimuli were given at irregular intervals, with at least 5 s between each stimulus. EMG recordings were made using surface Ag/AgCl electrodes fixed over the muscles of interest. Signals were amplified by Devices 3160 preamplifiers with filters set at 80 Hz and 2.5 kHz (3 dB points) and by a further Devices 3120 amplifier. These restricted filter settings were chosen to allow inclusion of some older data collected with these characteristics. Data were collected and stored on floppy disc by a PDP 12 computer with a sampling frequency of 5 kHz per channel. Each recorded potential was displayed on the visual display unit and the latency and duration of the muscle action potentials were measured by visual inspection of the raw EMG traces. The peak-to-peak size and area of each potential was measured by the computer.

Cortical somatosensory evoked potentials were recorded to 3 Hz stimulation of the median nerve at the wrist with an intensity just above threshold for a visible twitch of the thumb. 128 trials were averaged, using linked mastoid reference electrodes. Filter settings were 8 Hz and 2.5 kHz (3 dB points).

The following procedures were used in the detailed studies.

### *Location of stimulating electrodes*

When investigating the optimal site for stimulation of the limb areas of the motor cortex, a large number of electrodes were fixed to the scalp in 6 subjects. The effects of anodal and cathodal stimuli were examined at various sites. For the arm muscles the cathode was placed at the vertex and the

location of the anode varied randomly between the remaining electrodes without the subjects' knowledge. For the leg muscles the cathode was placed anterior to the vertex while the anode location was varied around the vertex. Stimuli were given whilst at rest and when the subject maintained a constant small (about 10% maximum) voluntary contraction of the muscle being studied. An EMG display was given as reference. Five stimuli at various intensities were applied at each electrode position.

#### *Stimulation of relaxed muscles*

Having determined the optimal sites for stimulation of the arm and leg muscles, the characteristics of the EMG responses in different muscles were investigated at various stimulus intensities. Four individuals were selected for these studies, chosen for their ability to remain totally relaxed (monitored by surface EMG) throughout the procedures. Five stimuli were given at each randomly chosen intensity from subthreshold to maximum. Recordings were made from the first dorsal interosseous (FDI), abductor pollicis brevis (APB), the long flexors and extensors of the fingers and wrist, biceps and deltoid muscles in the arm, and from the extensor digitorum brevis muscle (EDB) of the leg.

#### *Stimulation of active muscles*

In these experiments the subjects ( $n=10$ ) were instructed to maintain a constant level of gentle background voluntary activity (approximately 5–10% maximum) in the muscle under study. The muscles studied and the methods used were identical to those described in the above experiment.

In 3 subjects, the effect of the level of the force exerted by the contraction was studied in more detail in the first dorsal interosseous muscle. The subjects maintained an isometric contraction of this muscle by abducting the index finger against a strain gauge attached to the proximal interphalangeal joint of the index finger. The hand was pronated with the other fingers, thumb and wrist firmly fixed to prevent them assisting the FDI. A visual display of contraction force was given to the subjects (see Stephens and Taylor, 1972). Different intensities of stimulus were intermixed at random.

#### *Estimation of corticomotoneuron conduction velocities to cervical segments of the spinal cord*

Stimulation over the cervical spinal cord, with the same stimulating device, was used to obtain an estimate of the peripheral conduction times to the same muscles examined by cortical stimulation. The stimulating electrodes were placed with the cathode over the spinous process of the seventh cervical vertebra, and the anode 5–6 cm proximal in the midline. The EMG responses were recorded from the same muscles examined by cortical stimulation, and were recorded in the same fashion. Stimulation voltage was increased until minimum latency responses were obtained. The latency to onset of EMG activity after stimulation over the cervical segments of the spinal cord produced an approximation of the total peripheral conduction time. This was then subtracted from the latency to onset of EMG activity in the same muscles after cortical stimulation to give some estimate of the central motor conduction time. Spinal stimulation in this way is believed to activate the motor roots at their exit from the spinal canal (Mills and Murray, 1986). We did not estimate central conduction times to lumbar segments of the spinal cord.

In order to calculate the conduction velocity in the corticomotoneuron tracts, some estimate of the distances these pathways traverse was required. We have taken the values of 240 mm and 210 mm quoted by Desmedt and Cheron (1983) as an approximation of the distances from the cerebral cortex to the T1 and C6 segments of the cord, respectively.

## RESULTS

Using the stimulating electrode positions suggested by Merton and Morton (1980), we found that stimulation over one cerebral hemisphere (with the cathode at the vertex and the anode at 7 cm lateral to it on a line drawn from the vertex to

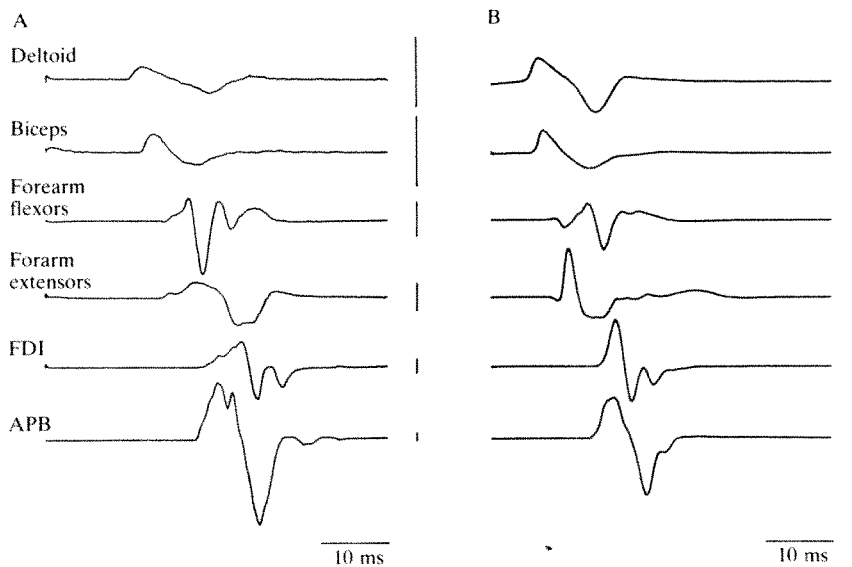


FIG. 1. A, EMG responses in the relaxed arm muscles of a normal subject after a single anodal stimulation of the contralateral motor cortex at 90% of the maximum output of the stimulator. The stimulus was delivered 7 cm lateral to the vertex, on a line drawn from the vertex to the external auditory meatus, corresponding to the hand area of the motor cortex. The cortical stimulus was given at the start of the trace. The vertical calibrations equal 0.2 mV. This means that the responses were by far the largest in distal muscles. Note the latency differences between proximal and distal muscles. B, EMG responses in the same muscles to stimulation over the cervical spinal cord. The stimulus was given at the start of the sweep. Vertical calibrations are equivalent to 10 mV. A single trial is shown in both A and B. In this and subsequent figures, upwards deflection in EMG records represents negativity at the active electrode.

the external auditory meatus) can produce activity in all the contralateral arm muscles studied (deltoid, biceps, forearm flexors and extensors, APB and FDI) at short latency. The responses from a single trial in a relaxed subject are illustrated in fig. 1. This shows that the largest EMG responses (both in absolute terms and as a percentage of maximal peripheral M wave amplitude, *see below*) were recorded in the distal muscles and there was an orderly progression of latencies from the proximal to the distal muscles.

#### *Effect of electrode polarity*

To examine the effect of polarity of the stimulating electrodes, one anode and one cathode of equal size were placed symmetrically on opposite sides of the head. When the anode was placed over the right motor cortex and the cathode over the left motor cortex, a large EMG response was seen in the left APB muscle. Reversal of the polarity of the stimulating electrodes produced a larger EMG response in the right APB (fig. 2). The largest responses were therefore recorded in the muscles contralateral to the anode, suggesting that the motor cortex was activated preferentially by anodal stimulation.

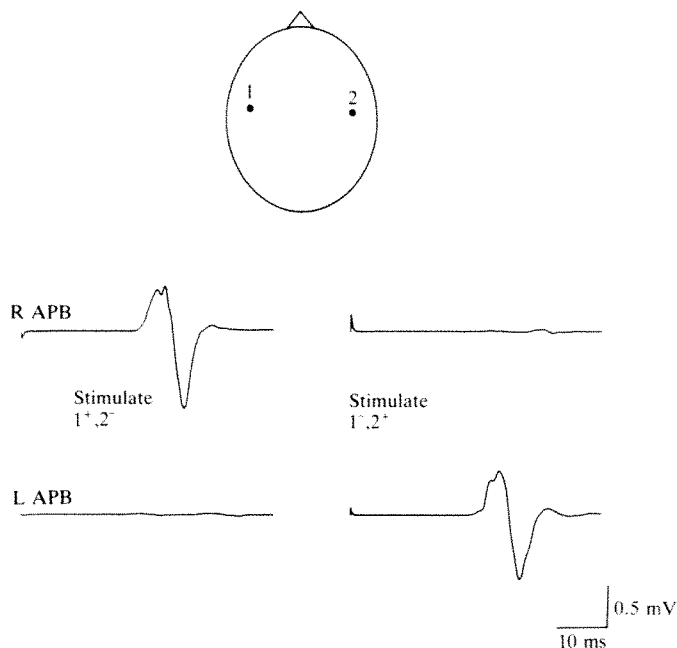


FIG. 2. EMG responses of APB recorded from right and left hands after bipolar stimulation (at an intensity just above the motor threshold) with electrodes placed on either side of the head (corresponding to the hand areas of the motor cortex). Each response is the average of 10 trials in one subject (relaxed). Note that at these low intensities, stimulation occurs under the anode, and that reversal of electrode polarity reverses the side of the muscle response.

### *Effect of moving the cathode*

Although stimulation occurred preferentially at the anode, changing the scalp location of the cathode also could affect the size of the EMG responses. Fig. 3A illustrates the effect of moving the cathode coronally across the head, while maintaining the anode over the lateral part of the right motor cortex. With the cathode placed symmetrically over the left lateral motor cortex the peak-to-peak size of the EMG response in the left APB was 2.14 mV. As the cathode was shifted towards the anode the size of the EMG response diminished (To 2.0 mV, 1.21 mV, 0.04 mV).

### *Localization of the stimulus and effects of electrode position*

A question of immediate importance was the extent to which the cortical stimulus could be focused in order to stimulate selectively different areas of the motor cortex. For example were there critical positions of the stimulating electrodes that would permit the selective activation of a single muscle? In general this has not been our experience. However, some crude localization was evident. With strategic placement of the stimulating electrodes it was possible to excite all the contralateral arm muscles without producing responses in the leg muscles and vice versa. Nevertheless,

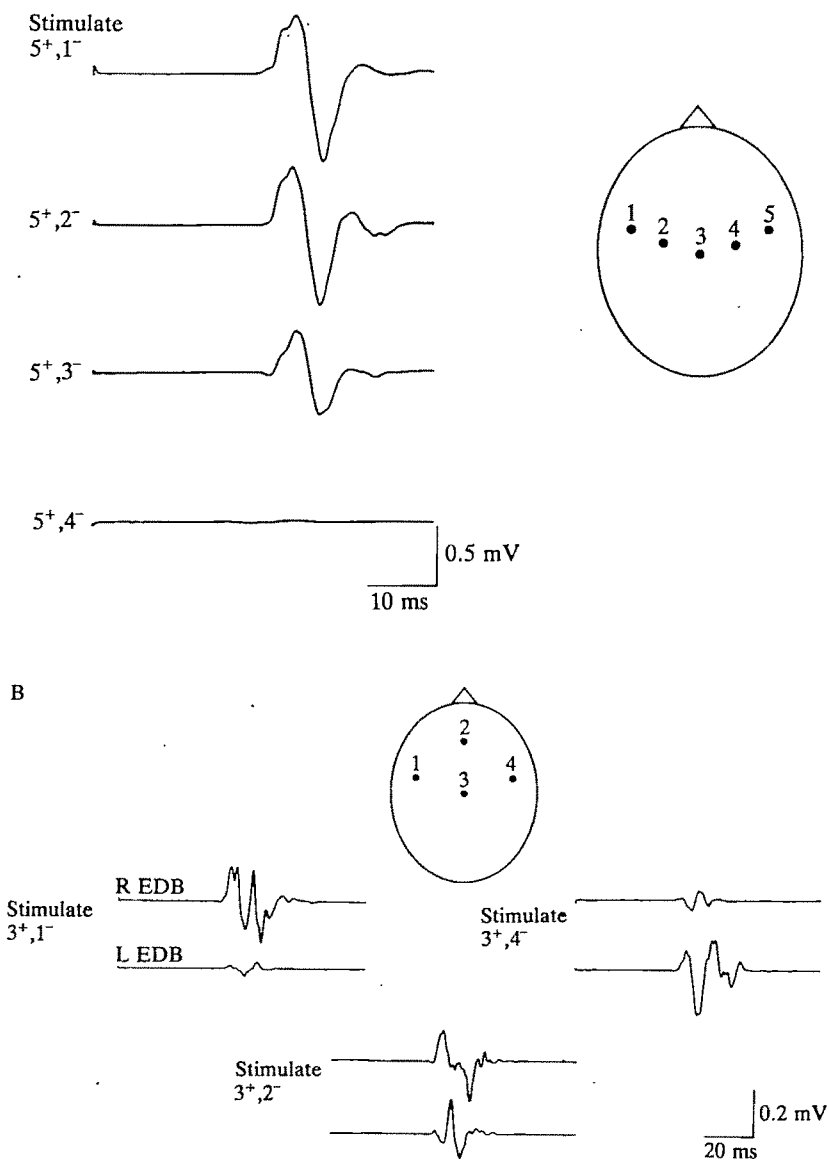


FIG. 3. A, EMG responses from the relaxed left APB muscle following anodal cortical stimulation at 70% of the maximum stimulus intensity, at the hand area of the right motor cortex (position 5). The cathode was varied from positions 1 to 4. Each trace represents the average of 10 trials in a relaxed subject. As the cathode was moved closer to the anode, the response size decreased (see text for details). B, EMG responses recorded bilaterally from the relaxed EDB muscle following anodal cortical stimulation at 90% maximum. The traces illustrate the effect of moving the cathode whilst the anode remains at the vertex (location 3). When the cathode is 6 cm anterior to the vertex (location 2), responses are recorded bilaterally. When the cathode is 7 cm lateral to the vertex (locations 1 and 4), the response is predominantly contralateral. Each trace is the average of 5 trials.



in some subjects, both upper and lower limbs could be activated by stimuli of sufficiently large intensity.

Although focal stimulation of a single muscle was not possible, the site of the stimulating anode did influence the extent to which certain muscles were activated. In some subjects moving the anode in a mediolateral direction over the scalp revealed a somatotopic representation as anticipated from stimulation of the exposed cortex in man and primates. As reported by Rossini *et al.* (1985b) using a different stimulating montage, shifting the anode medially (towards the vertex) increased the size of the proximal EMG muscle responses and decreased the size of the distal hand muscle responses. (To avoid the possibility that this effect was due to changes in the interelectrode distance we maintained a constant interelectrode distance of 7 cm in the course of this experiment.) For the hand muscles, movement of the anode in an anteroposterior direction (with the cathode at the vertex) revealed that the largest EMG responses (with the lowest stimulation threshold) were recorded at a point 7 cm lateral to the vertex on a line joining it to the external auditory meatus. This optimal stimulating site for the hand was some 2 to 4 cm anterior to the position at which the largest cortical SEP (N20 component) was recorded following stimulation of the contralateral median nerve at the wrist (fig. 4).

When recording from the leg muscles (quadriceps, tibialis anterior, soleus, extensor digitorum brevis), the optimal position of the stimulating anode was at the

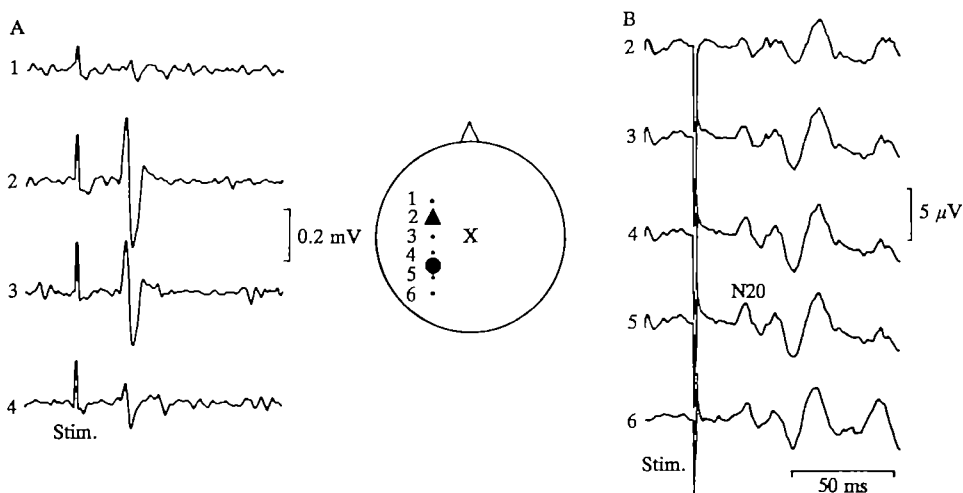


FIG. 4. A, single EMG responses in the left APB recorded after contralateral anodal cortical stimulation at 50% of maximum (cathode at vertex (X)), at different positions in the anteroposterior plane in a subject maintaining a gentle background contraction (approx. 10% maximum) of the APB muscle. B, average cortical somatosensory evoked responses ( $n = 128$ ) recorded from the same electrodes (with linked mastoid reference) after stimulation of the contralateral median nerve just above motor threshold at the wrist. Note that in A the muscle action potential is largest at position 2 (▲), which is probably slightly forward of the central sulcus, whereas in B the N20 amplitude (representing the arrival of the afferent sensory volley in the cortex) is largest posterior to it (electrodes 4 and 5) (●). The timing of the stimuli (stim.) can be gauged from the stimulus artefact.

vertex (roughly overlying the leg area of the motor cortex) with the cathode 6 to 7 cm anterior to it, in the midline. At this site the leg muscles were activated bilaterally. If the cathode was placed 7 cm lateral to the vertex, the EMG responses in the legs were predominantly contralateral (fig. 3B). Shifting the anode in an anterior and posterior direction indicated that the exact location near the vertex for obtaining maximal EMG responses in the legs varied between different subjects.

In most of the experiments reported in these papers our usual sites of stimulation were as follows. For the muscles in the arm, the cathode was placed at the vertex and anode 7 cm lateral. To stimulate muscles bilaterally in the legs, we used a vertex anode with the cathode placed 6 cm anterior.

### *Characteristics of responses in relaxed muscles*

For any given intensity of anodal cortical stimulus there was a large variation in the size of EMG responses which could be elicited at rest in different individuals. In the majority of subjects, the threshold stimulus for relaxed hand muscles was some 50 to 60% of the maximum stimulus intensity (i.e., about 350 V, with a time constant of 50  $\mu$ s). In addition to the differences between subjects, the thresholds could also vary in the one individual on different occasions. The response threshold was lowest for intrinsic hand and forearm extensor muscles and highest for the proximal arm muscles (figs 5 and 6). The relaxed leg muscles had a higher threshold for activation than arm muscles, requiring of the order of 60 to 80% maximum. This threshold difference could be demonstrated only if all the muscles in the limb were totally relaxed. Minimal activation of any muscle group could change its threshold dramatically (*see below*).

Increasing the intensity of anodal cortical stimulation increased the size of the EMG potentials, but for any given intensity, the largest responses always were found in the distal muscle groups. In most subjects the peak-to-peak size of responses in these muscles reached maximal values before maximal stimulation intensity was reached (figs 5, 6, FDI). When saturation occurred, the maximum response size in muscles of the upper limb was less than 70% (and often less than 50%) of that of the maximum M wave (measured either peak-peak or area) following supramaximal peripheral nerve stimulation. As the EMG response increased in size, with increasing intensities of anodal cortical stimulation, its duration became longer (figs 5, 7). At maximum cortical stimulation strength, the duration was at least twice as long as that of the maximum M wave produced by supramaximal peripheral nerve stimulation.

In addition to these changes in amplitude and duration, the strength of anodal cortical stimulation could also affect the latency of the EMG responses while the subject was at rest. In both upper and lower limb muscles the average latency at maximum stimulation strength could be up to 4 ms shorter than its value at threshold (fig. 7, APB). At any given stimulus intensity there was some variation in latency of individual consecutive potentials when a large number were collected. This was most commonly of the order of 2 to 4 ms (*see following paper*). Similar

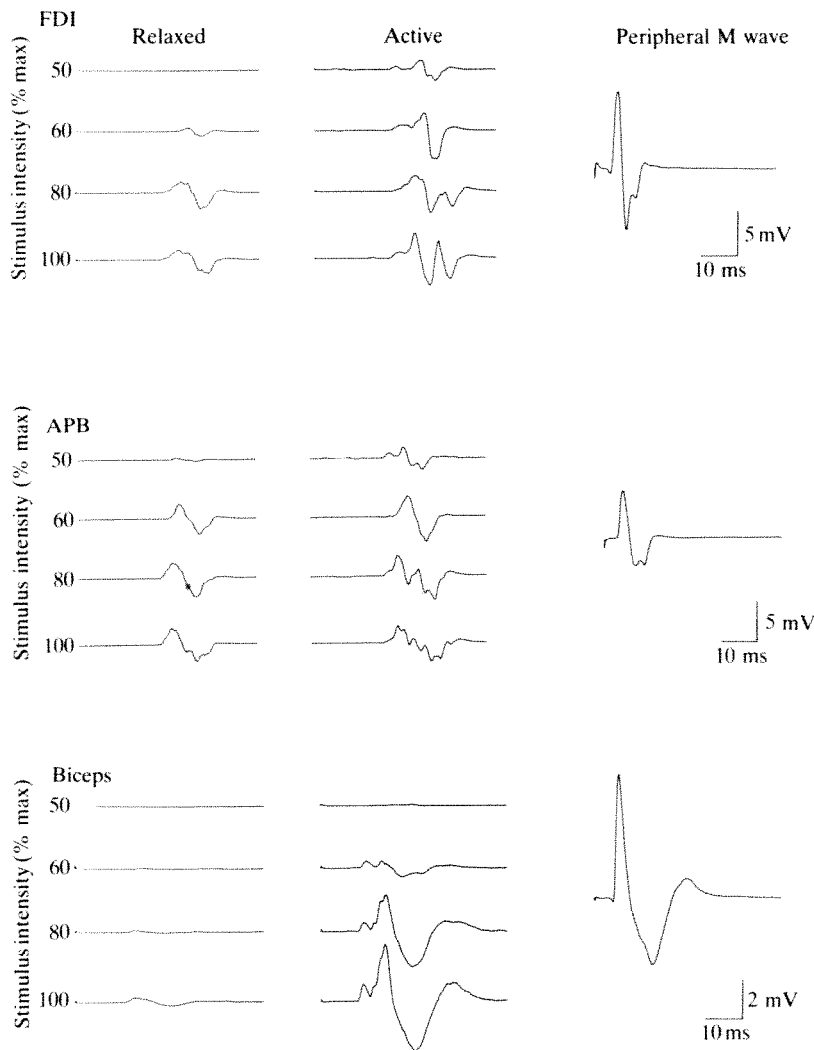


FIG. 5. A series of EMG responses in three different muscles of the arm (FDI, *upper section*; APB, *middle section*; biceps brachii, *lower section*) following anodal cortical stimulation over the contralateral hand area of cortex. The subject was completely relaxed (*left columns*) or was activating the muscles voluntarily to about 10% of maximum (*middle columns*). These responses can be compared with the supramaximal peripheral M waves produced in the same muscles (*right columns*) by stimulation of the ulnar nerve at the wrist (FDI), median nerve at the wrist (APB), and Erb's point (biceps). As the stimulus intensity was increased (from 50–100% maximum), the size of the EMG responses increased in both active and relaxed muscles. In the two hand muscles, the peak-to-peak size of the potentials saturated at the highest stimulus intensities, and never attained the size of the peripheral M wave. Note, however, that the responses following cortical stimulation can be extremely polyphasic, especially in active muscles at high intensities of stimulation. The duration of the responses under these conditions is more than twice that of the peripheral M wave. EMG responses are longer, and the stimulus threshold is lower in active than in relaxed muscles. In addition, it can be seen that biceps has a far higher threshold for activation from the cortex than either FDI or APB. Minimal latencies to EMG onset were: FDI, 23 ms (relaxed) and 20.8 ms (active); APB, 22.8 ms (relaxed) and 21 ms (active); biceps, 13.5 ms (relaxed) and 10 ms (active). These responses are single trials taken from a series in which cortical stimulation intensities were intermixed at random, and were given without warning every 10–20 s. Averaging a series of trials would tend to smooth out the polyphasic nature of these responses.

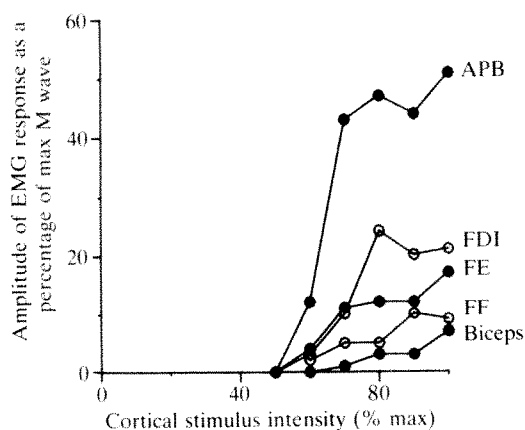


FIG. 6. Peak-to-peak size of EMG responses to anodal cortical stimulation at different stimulus intensities (expressed as a percentage of maximum output of the stimulator) in 5 different muscles of the arm in a normal relaxed subject. All responses were recorded at rest. The size of the EMG response has been expressed as a percentage of the maximum M wave size of the same muscles obtained by supramaximal peripheral nerve stimulation. Each point represents the average of 5 responses. Responses in intrinsic hand muscles are larger and have lower thresholds for activation than those in more proximally situated muscles. FF, FE = flexor and extensor muscles in the forearm.

variations in the latency, size and duration of the EMG responses were seen in the proximal and distal muscles.

This variability of the response size and latency was observed in all muscles studied at rest. In general the smaller responses tended to occur at longer latencies. The latency and size differences also were crucially dependent on the degree of relaxation, for even the slightest tensing of the target muscle could significantly shorten its latency, as will be discussed below.

#### *Characteristics of responses in active muscles*

Voluntary contraction of the target muscle had three important effects: (1) voluntary activity reduced the threshold intensity of cortical stimulation at which EMG activity could be evoked; (2) at any given intensity, responses were larger in the active muscle than in the relaxed muscle; and (3) the latency of responses in the active muscle was shorter than in the relaxed state.

The lowering of the response threshold by voluntary contraction of the target muscle was evident in all muscles studied (figs 5, 7). Very subtle changes in the level of the background muscle activity were capable of producing this effect; for example, even slight activation of the proximal muscles of the upper limb in the course of postural maintenance while seated would lower their response threshold. The size of the EMG responses increased as the intensity of cortical stimulation was increased. In the contracting muscle, however, the size of the EMG responses produced by a stimulus just greater than threshold could approach the maximum size that was achieved in a relaxed muscle. The duration of the compound muscle action potential increased with cortical stimulus strength and in general was longer

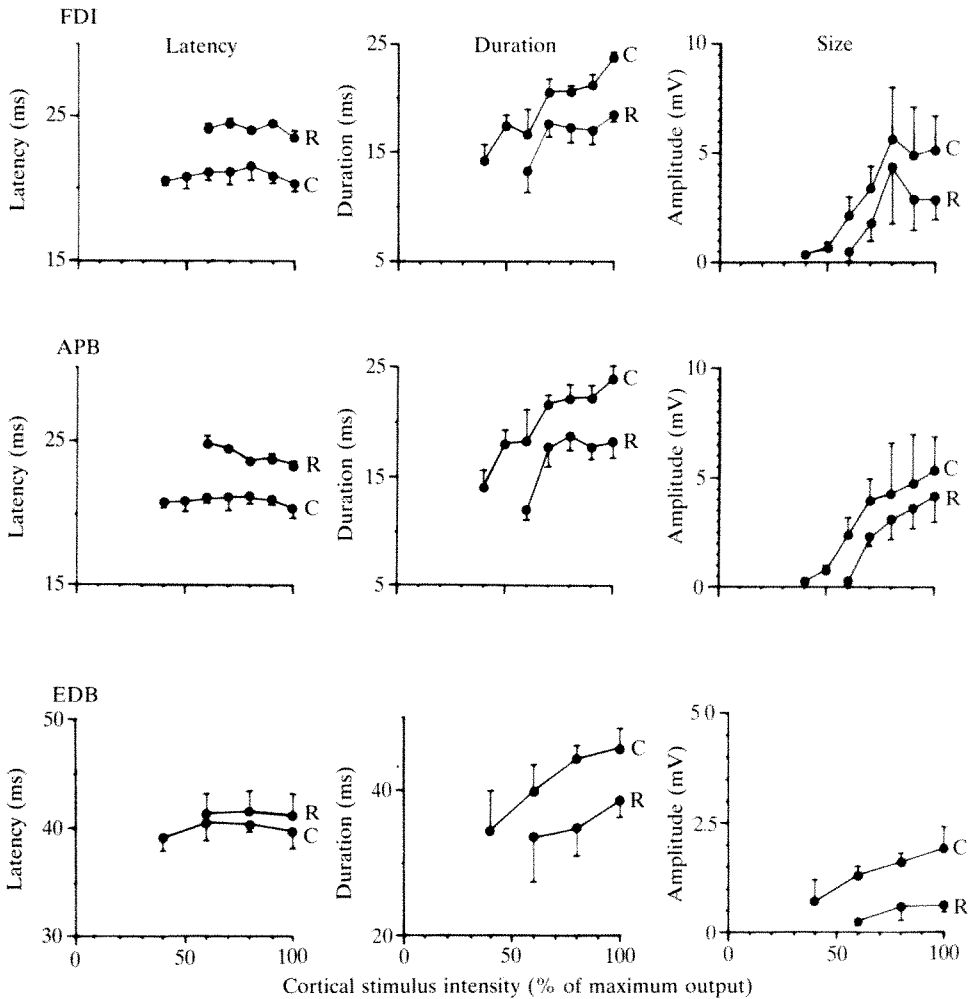


FIG. 7. Latency, duration and peak-to-peak size of the EMG responses to anodal cortical stimulation for the FDI and APB in the arm, and EDB in the leg at increasing stimulus intensities (expressed as a percentage of maximum output of the stimulator). The arm responses were obtained with the anode over the hand area of the motor cortex and the cathode at the vertex. The leg responses were obtained with the anode at the vertex and the cathode 6 cm anteriorly. EMG responses were obtained in the relaxed (R) and contracting (C) muscles. Each point represents the average of 15 responses in 3 normal subjects ( $\pm 1$  SE). The response latency tended to shorten with increasing stimulus intensity in relaxed muscles. When the muscle was contracting, the threshold stimulus strength decreased and the response latency became significantly shorter, but did not change with the intensity of stimulation. The response size and duration increased with increasing stimulus intensity, but were always larger in the contracting muscle.

than that recorded from relaxed muscles (*see* figs 5, 7). This lengthening of response duration was accompanied by an increase in the complexity of the EMG waveform, which was particularly evident in the contracting muscle at high stimulus intensities (*see* fig. 5, FDI and APB). Distal and proximal muscles showed similar changes with voluntary contraction, with the major difference again being the larger size of the distal muscle responses.

The latency to onset of the EMG responses in active muscles were 2 to 6 ms shorter than those recorded in relaxed muscles at the same intensity of stimulation (fig. 5), in both the proximal and distal muscles of the upper and lower limbs. Unlike the relaxed state, however, there was little effect of stimulus intensity on the latency of the response in contracting muscles (fig. 7).

The size of EMG responses varied considerably in both relaxed and active muscles at all cortical stimulation intensities. Even when comparing responses of equal size, the latency when the muscle was active was considerably shorter than when relaxed. On rare occasions, however, individual responses in the relaxed muscle had the same latency as those when active.

The decrease in latency with voluntary contraction in both distal and proximal muscles often was due to the appearance of a low threshold early wavelet at the onset of the EMG response. Increasing the stimulus intensity increased the amplitude of the later parts of the EMG potential while leaving the size of the early wavelet relatively unchanged (fig. 5). Such additional wavelets were never seen in responses elicited by increasing strengths of direct stimulation of peripheral nerves.

In 3 subjects the effect of contraction strength on the characteristics of the response to scalp stimulation was examined. Once the muscle was active the strength of contraction (10 or 50% maximal voluntary effort) had little or no effect on threshold or the latency of the response. However, increasing the level of

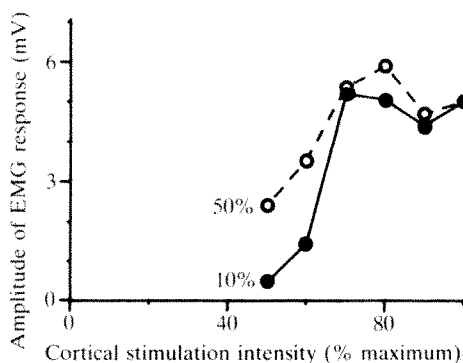


FIG. 8. The effect of two different levels of background force (10 and 50% maximum voluntary activation) on the peak-to-peak size of EMG responses in the FDI at increasing intensities of anodal cortical stimulation of the contralateral motor cortex (expressed as a percentage of the maximal output of the stimulator). Each point represents the average of 5 trials from 1 subject. At the two lowest stimulus intensities, the response was smaller with low levels of background contraction. However, once a critical stimulus intensity was reached (about 70% of maximum) all responses approached maximal levels.

voluntary activity produced larger responses for a given intensity of anodal cortical stimulus until the response reached its maximum size. The maximal size of the response was reached at approximately the same stimulus intensity for all levels of background contraction (fig. 8). This stimulus intensity was also the same in the resting muscle, although the maximal size of response in relaxed muscle was smaller than in active muscle.

### *Reproducibility of responses*

Repeated observations have been made on each of the authors over periods of five years. By far the most consistent parameter from one recording session to the next was the minimum response latency in active muscles. The maximum variation was usually 0.5 ms in any one subject. Size of response was not so stable, even under relatively controlled conditions of constant isometric contraction. From session to session the amplitude of the average response varied by up to 100% in each subject. We presume that major contributing factors to this variability were small differences in the precise level of background activity and electrode placement from day to day. Response latency in relaxed muscles was more variable than in contracting muscles (*see following paper*), and was accompanied by larger changes in the size of the EMG response. We suggest that these effects were due mainly to subthreshold variations in the excitability of spinal alpha-motoneurons.

### *Estimation of corticomotoneuron conduction velocities*

The mean latencies ( $\pm 1$  SD), in 10 subjects, to onset of EMG potentials after anodal cortical stimulation in the voluntarily contracting (approximately 10% of maximum) biceps and thenar muscles were  $10.0 \pm 0.8$  ms and  $19.6 \pm 1.0$  ms, respectively. The latencies to onset in the same muscles (in the same subjects) after stimulation over the cervical spinal cord were  $5.8 \pm 0.6$  ms and  $14.4 \pm 1.0$  ms, respectively. If the fastest motoneurons involved in the muscle response to either form of stimulation conduct at similar velocities then subtraction of spinal from cortical latencies gives an estimate of the central motor conduction time. The mean estimates of the central conduction times ( $\pm 1$  SD), calculated in each subject, were  $4.1 \pm 0.6$  ms for the biceps and  $5.0 \pm 0.6$  ms for the thenar muscles. Since spinal stimulation may occur up to 4 cm distal to the spinal motoneurons (Mills and Murray, 1986), then this figure includes the time taken to traverse the corticospinal pathway, plus the synaptic delay at the motoneuron and conduction over a short segment of peripheral nerve.

From these data it is possible to estimate the corticospinal conduction velocity, although a number of extra assumptions are required. If we assume (1) a mono-synaptic connection from cortex to spinal motoneurons, (2) 1 ms conduction time to allow for synaptic plus peripheral delays, and (3) that the distance from the site of stimulation in the brain to the C6 and T1 segments were 210 and 240 mm, respectively (*see Methods*), the approximate corticospinal conduction velocities to these segments were of the order of  $65 \text{ m} \cdot \text{s}^{-1}$ .

The test has now been used on over 100 subjects and patients in our laboratory. To the best of our knowledge there have been no short or long term adverse or untoward effects of cortical stimulation. In addition, repeated shocks have been delivered to all the authors during experimental studies on numerous occasions, with the only inconvenience being the scalp pain caused by the stimulus. This level of discomfort was acceptable to all subjects whom we studied.

## DISCUSSION

Electrical stimulation of the human brain through the scalp can give rise to motor responses at short latency in contralateral muscles of the body. The major questions which arise from this observation and which are of critical importance to the application of the technique in clinical practice are (1) where in the brain is stimulation taking place, and (2) by what pathways are impulses conducted to the spinal motoneurons?

### *Site of stimulation and pathways mediating responses*

The site of stimulation appears to be at or near the motor cortex. The basic finding was that arm muscles were preferentially activated with lateral placement of the anode, whereas the best position for activation of leg muscles was with the anode at the vertex. In addition, it was possible to demonstrate a somatotopic localization of the proximal and distal muscles of the upper limb. This was a subtle finding, with different electrode positions producing relative changes in the size of the evoked muscle response. Similar findings have been reported by Rossini *et al.* (1985*b*) using a different stimulating montage. Unless stimulation was occurring at or near the cerebral cortex, such localization would be unlikely to occur. The greater efficacy of anodal over cathodal stimulation also is consistent with stimulation of cortical or immediately adjacent subcortical structures. That anodal stimulation is superior to cathodal for activation of the exposed motor cortex in the monkey has been recognized since the time of Ferrier (1875).

The effects of motor cortical stimulation on spinal motoneurons probably are mediated by many direct and indirect descending pathways. However, there is good evidence that the pathway responsible for the onset of EMG activity is composed of fast conducting fibres of the corticomotoneuronal component of the corticospinal tract. The estimate of corticospinal conduction velocity after cortical stimulation was of the order of  $65 \text{ m}\cdot\text{s}^{-1}$ . As pointed out, a number of assumptions have to be made to arrive at this figure, but it is very comparable with that obtained in the largest and fastest corticomotoneuronal elements studied in the monkey (Bernhard and Bohm, 1954; Kernell and Wu Chien-Ping, 1967). Similar values have been estimated previously in man (Marsden *et al.*, 1982; Rossini *et al.*, 1985*a*, Boyd *et al.*, 1986). Unfortunately, because so many assumptions are required to calculate corticomotoneuron conduction velocity by the techniques employed here, it prob-



ably is not a useful parameter to use in clinical studies. The simple latency to onset of the response in active muscles is easier to define and may suffice.

The latency of the responses in the *contracting* whole muscle, for all intensities of cortical stimulation, was remarkably stable, varying by no more than 1 to 2 ms over a series of single trials. In addition, in the following paper we show that the mean variation in latency of single motor unit discharge in a *contracting* muscle after cortex stimulation is only 1.8 ms. This is compatible with the intervention of only one or two synapses between the cortical output neuron stimulated and the neuromuscular junction, at least in the case of the arm. In view of the increasing importance of the monosynaptic component of the corticospinal tract in higher primates (Phillips and Porter, 1977), this suggests that the fastest pathways in man may also be monosynaptic in addition to being rapidly conducting.

This is not to suggest that other descending pathways may not be activated by the cortical stimulus, either directly or synaptically. For example, impulses in other pathways may contribute to the later phases of the compound motor action potential. The reticulospinal tract has both monosynaptic and polysynaptic connections with the spinal cord. It may conduct rapidly in animals, but is distributed bilaterally to innervate predominantly proximal muscles (Peterson *et al.*, 1979), in contrast to the pathways recruited in the present study. The lateral vestibulospinal pathways are also monosynaptic and polysynaptic, may conduct rapidly, but innervate the spinal cord predominantly ipsilaterally (Nyberg-Hansen and Mascitti, 1964). In man, our knowledge of descending motor pathways other than the pyramidal tract is rudimentary (Nathan and Smith, 1955). There is no evidence that the rubrospinal tract exists in man in functional proportions (Nathan and Smith, 1982), while little is known about the interstitiospinal or tectospinal tracts. We would therefore suggest that in our present state of knowledge, the term corticomotoneuron (introduced by Bernhard and Bohm in 1954) is the most accurate description of the pathways mediating the earliest effects of cortical stimulation.

#### *Problems in defining the precise point of stimulation in the cortex*

Although it has been possible to record responses in all normal human subjects studied to date in both contracting and relaxed muscles, there may be quite large differences between the thresholds for muscle activation and the maximal sizes of EMG responses between individuals. In most subjects the stimulus strengths required to activate leg muscles were 10 to 30% higher than those for the arm. The proximal muscles of the arm also require slightly higher stimulus strengths than distal muscles. The observation that responses were largest and the threshold for activation lowest in the distal musculature, particularly in the arm, is in accord with the theory of 'preferential accessibility of the distal muscles', described for monopolar anodal cortical stimulation in the primate (Phillips and Porter, 1977). However, as these authors indicate, the effects of bipolar stimulation (as we have used) may be much more complex than those of unipolar anodal stimulation. Thus interpretation of the distribution of responses when stimulating at different sites

must take several factors into account. These relate principally to uncertainties about the distribution of the electric current within the brain after bipolar stimulation. For example, we have little knowledge of the extent and pattern of spread of the electrical stimulus within the skull and brain. Furthermore, the thickness and resistance of the skin and skull, and the distance and orientation of the motor cortex and its neurons from the stimulating electrodes may all contribute to the minor variations seen among normal individuals. The limitations of attempts to localize accurately areas of the cerebral cortex with respect to the surface markings of the skull have previously been emphasized (Bates, 1951). It is therefore difficult to comment on the slight differences in thresholds and variations in response size among different subjects. These considerations also make it difficult to comment on the pattern and density of corticomotoneuron projection to different muscles in man on the basis of the distribution and size of the EMG responses to cortical stimulation. However, the preferential activation of the distal arm muscles would be explained by their larger EPSPs and the preponderance of projections to them (Kuypers, 1960; Clough *et al.*, 1968).

#### *Effects of voluntary activation and stimulation strength*

Accepting that the earliest component of the EMG responses in a contracting muscle to cortical stimulation represents the activation of the fastest (and monosynaptic) corticomotoneuron pathways, the next questions are what mechanisms are responsible for the changes in response size and duration with increasing strengths of cortical stimulation and the differences between relaxed and contracting muscles?

The size of the EMG response was larger at all intensities of cortical stimulation and the threshold lower when the muscle was made to contract. Voluntary contraction could achieve this effect either by increasing spinal cord excitability so that a given intensity of cortical stimulus might result in a greater spinal output, or by increasing the cortical excitability so that the same intensity of cortical stimulus might generate a larger descending volley (than when relaxed). Another feature of the present results was that the maximal peak-to-peak size of the EMG response following cortical stimulation usually was less than 50% of that of the maximal peripheral M wave, while the duration of the potential could be two or more times longer than that of the M wave. Dispersion of the descending volley in both peripheral and central pathways might contribute to the smaller size, longer duration and greater waveform complexity of the maximal EMG responses to cortical stimulation. However, it is also possible that a single cortical shock could produce multiple descending volleys of excitation which might repetitively discharge the spinal motoneurons (Marsden *et al.*, 1983). Finally, the effect of voluntary contraction on the latency of the EMG responses to cortical stimulation was to shorten dramatically the latency of the response when compared with the relaxed muscle. Since voluntary contraction increased the size of responses, one explanation for

the decrease in response latency with contraction may have arisen from the size principle of motor unit recruitment (Henneman *et al.*, 1965). The cortical volley may first recruit small slowly conducting motoneurons, but as the response size increases, larger and faster units might be recruited, with a concomitant decrease in latency. However, if a single cortical stimulus evoked multiple descending excitatory volleys, then these may also contribute to the latency changes in the relaxed muscle.

These possibilities are the subject of enquiry in the following paper.

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# MOTOR CORTEX STIMULATION IN INTACT MAN

## 2. MULTIPLE DESCENDING VOLLEYS

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### SUMMARY

Using an isometric strain gauge, we measured the twitch force produced in the first dorsal interosseous (FDI) muscle by a single anodal shock to the contralateral scalp. At high intensities of stimulation this twitch can greatly exceed the force produced by supramaximal stimulation of peripheral nerve. This indicates that a single cortical shock can cause repetitive firing of some or all FDI motoneurons. Such repetitive firing was demonstrated using a collision technique in which a supramaximal ulnar nerve stimulus was given at the wrist shortly after a cortical shock. The antidromic volley from the peripheral nerve stimulation failed to obliterate completely the response to cortical stimulation. Additional EMG activity was visible in the normally silent period between ulnar M and F waves. This activity must have been due to the presence of repetitive volleys of activity set up in spinal motoneurons by the cortical shock. Such activity summates with the twitch produced by the ulnar M wave to produce a very large force twitch of the muscle. Multiple firing of some motoneurons can be observed in some individuals at cortical stimulation intensities below that necessary to evoke activity in all the motoneurons in the FDI pool.

Multiple firing probably was caused by repetitive excitatory inputs impinging on spinal motoneurons. These could be demonstrated using poststimulus time histogram techniques on single motor units. Low intensities of cortical stimulation produced a single short duration (mean 1.8 ms) peak of increased motor unit firing 20 to 30 ms after the shock. At high intensities, this was followed by extra peaks some 4 to 5 ms later. H reflex testing showed that the threshold of the initial descending volley produced by the cortical stimulus was uninfluenced by a voluntary contraction.

These results are discussed with reference to the D and I waves recorded from pyramidal tract after anodal stimulation of the exposed cortex in animals.

### INTRODUCTION

In the previous paper (Rothwell *et al.*, 1987), the characteristics of EMG responses produced by percutaneous stimulation of the human motor cortex with a single short duration anodal electrical stimulus were described. Three important phenom-

ena emerged from these data, two of which relate to changes in the muscle response when the subject exerted a background voluntary contraction. First, when a muscle was activated voluntarily, a given intensity of cortical stimulus produced a much larger response than that seen in the relaxed muscle. Secondly, the latency of the EMG response was substantially shortened under these circumstances. In addition, the duration of the EMG response following cortical stimulation in either relaxed or active muscles could be far longer than a maximal peripheral M wave. The present experiments were designed to investigate these phenomena and shed light on the underlying mechanisms. Part of these data has appeared in abstract form (Berardelli *et al.*, 1985; Day *et al.*, 1986).

## METHODS

The experiments were performed on a total of 8 normal volunteers including 6 of the authors. Electrical stimuli to the scalp were delivered by a prototype capacitive discharge device which was designed and built by Mr H. B. Morton (*see* Rothwell *et al.*, 1987, for details). Anodal stimuli were applied to the brain via two 9 mm diameter Ag/AgCl disc electrodes stuck onto the scalp with collodion glue. The cathode was placed at the vertex and the anode 7 cm down on a line joining the vertex to the external auditory meatus. The stimulus intensity has been expressed as a percentage of the maximum that the device could deliver (600 V with a decay time constant of 50  $\mu$ s). Electromyographic (EMG) responses were recorded from contralateral arm muscles via two 9 mm diameter Ag/AgCl disc electrodes taped over the belly of the muscle of interest, some 2 to 3 cm apart. EMGs were preamplified (Devices, type 3160), bandpass filtered ( $-3$  dB at 80 Hz and 2.5 kHz) and amplified (Devices, type 3120). A PDP12 computer collected the data with a sampling rate of 5 kHz, 2 kHz or 1 kHz per channel as appropriate. Data was then stored on floppy disc.

### *Latency changes of the EMG response*

Subjects were seated comfortably in a reclining armchair and received anodal cortical shocks at random intervals ranging from 5 to 20 s. EMG responses from first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles were recorded under two conditions: (1) with the subject completely relaxed and the muscles electrically silent, and (2) whilst exerting a small (approximately 5% maximum) background voluntary contraction of the muscles. To assist the subject in these tasks EMGs were displayed on oscilloscope screens. At each stimulus intensity fifty stimuli were given for both conditions.

### *Multiple firing of motoneurons*

These experiments were performed during isometric contraction of the FDI. Details of the force recording apparatus are described in the previous paper. Force output and surface EMG responses were recorded following cortical stimulation at different intensities or after supramaximal ulnar nerve stimulation at the wrist, while the subject exerted a known percentage (10%, 20%, 50%) of maximum voluntary contraction. Stimuli to the ulnar nerve were 0.5 ms pulses delivered from a Disa 15E07 nerve stimulator. The intensity was set to be 20% greater than that needed to produce a just-maximal M wave in FDI.

To investigate whether a single cortical stimulus was capable of causing some motoneurons to discharge more than once, we used a collision technique. Shortly after a cortical stimulus, the ulnar nerve was stimulated supramaximally at the wrist. It was assumed that the antidromic volley from this stimulus should collide with any orthodromic potentials set up in spinal motoneurons by the cortical shock. If only one orthodromic potential were conducted down each motoneuron, no EMG activity should be seen in FDI until at least the latency of a normal F wave (or longer). However, if

more than one orthodromic volley were set up in the same motoneurons by the cortical shock, the second (and subsequent) volley should not be affected by the collision, and would be able to produce EMG activity in the silent period between M and F waves. This extra EMG activity will summate with the ulnar M wave to produce a twitch force greater than that seen following ulnar nerve stimulation alone.

#### *Single motor unit studies*

The firing pattern of single motor units was studied in FDI using standard concentric needle electrodes. The units studied were all recruited at low force levels (less than 10% maximum) and fired tonically for periods of greater than 10 min. Audio feedback was provided to aid the subject in the task. Seven experiments were performed on 4 subjects. The time of occurrence of a particular motor unit potential was detected by a pulse height window discriminator designed by Mr H.C. Bertoya. If the height of the potential fell within two adjustable voltage levels then a 0.5 ms pulse was produced after a fixed delay of 4 ms. The motor unit potential and the upper and lower voltage level of the window were continuously monitored and the window was adjusted when necessary.

Anodal cortical stimuli were applied at random intervals (from 4–6 s) while the subject maintained a steady firing of a single motor unit in FDI at about 10 Hz. Surface EMG, needle EMG, and the discriminated motor unit pulse were recorded on magnetic tape using a Racal 7DS FM tape recorder to allow further analysis of the data.

#### *The mechanism of facilitation of the response to cortical stimulation during voluntary contraction*

In this experiment we examined whether the threshold intensity of an anodal cortical stimulus required to produce a descending volley was reduced by the subject voluntarily contracting the target muscle. In order to detect the arrival of a small descending volley at the spinal motoneuron pool we used H reflex testing. Previously we have shown that a single cortical stimulus, which is of insufficient intensity to produce a direct EMG response, may produce subthreshold excitability changes in spinal motoneurons (Cowan *et al.*, 1983, 1986). The time course and magnitude of these changes can be monitored by their effect on the size of H reflexes elicited at different times relative to the cortical stimulus. In wrist and finger flexor muscles of the forearm the earliest and largest effect was a facilitation of the H reflex. The peak facilitation occurred when the H reflex stimulus was delivered to the median nerve in the cubital fossa some 4 to 5 ms before the cortical stimulus. Because of the different times taken for the descending volley and the Ia volley to reach the motoneurons, a conditioning-test interval of –4 to –5 ms allows the Ia afferent volley and the descending volley to reach the spinal cord simultaneously. This conditioning-test interval only explores the influence of voluntary activity on the size of the volley responsible for the first phase of excitation of spinal motoneurons after cortical stimulation.

H reflexes were evoked in wrist and finger flexor muscles by delivering single low-intensity stimuli of 1 ms duration to the median nerve at the elbow (Day *et al.*, 1984). In random trials the H reflex was conditioned by a cortical stimulus using a conditioning-test interval of –4.5 ms (*see above*). At each cortical stimulus intensity, 8 control and 8 conditioned H reflexes were obtained. This was performed when the subjects ( $n=5$ ) were completely relaxed and the muscles silent, and when the subjects exerted a small background voluntary contraction (approximately 10% maximum) of the flexor muscle against an isotonic load offered by a torque motor. The size of control H reflexes under the two conditions were matched by adjusting the intensity of the median nerve stimulus. Different degrees of H reflex facilitation were obtained by changing the intensity of the cortical stimulus.

## RESULTS

*Latency changes of the EMG response to cortical stimulation*

As described in the previous paper (Rothwell *et al.*, 1987), slight voluntary activation (approximately 5% of maximum voluntary contraction) of the target muscle had a dramatic effect on the latency of the EMG response to cortical stimulation. Fig. 1A shows the distribution of response latencies recorded in the FDI and APB of one subject at different intensities of cortical stimulation. When relaxed, latencies were some 2 to 6 ms longer than when the muscles were active. Only in about 3% of the trials did the response latency in relaxed muscles jump to match that of active muscles. We attribute these rare short-latency responses to a failure of relaxation of the subject, a task which most subjects found difficult to achieve.

The same data are shown in fig. 1B, where the response latency has been plotted against the size of the EMG potential. This shows that the difference in latency between active and relaxed muscles was not due to differences in the size of the EMG response. Cortical stimuli up to 100% maximum were used when the subject was relaxed so that the range of size matched that seen when 70% maximum stimulation was given during voluntary activity. The graphs show that the latency of a given size of EMG potential could be 2 to 6 ms longer in a relaxed than in an active muscle. In relaxed muscles the EMG response latency varied by some 4 ms with the smallest responses tending to have the longest latency. Occasionally the response latency shortened in a stepwise fashion when the stimulus intensity was increased. An example of this is shown in fig. 1A for relaxed APB muscle when the stimulus intensity was increased from 90 to 100% of maximum output. This phenomenon could not be explained by an increase in response size since there was considerable overlap of size with responses at lower intensities (*see* fig. 1B).

*Multiple firing of motoneurons in response to single anodal cortical stimuli*

Fig. 2 illustrates the effect of increasing the cortical stimulus intensity on the EMG response and the twitch force of the FDI muscle. These records were obtained with the subject exerting an isometric background force of 10% maximal voluntary contraction. The figure shows that as the intensity of cortical stimulation was increased, the peak-to-peak size of the EMG response increased at first and then plateaued while the shape of the potential became more polyphasic. The twitch force, however, continued to grow in size and reached force levels greatly in excess of that produced by supramaximal stimulation of the ulnar nerve at the wrist. A similar phenomenon was noted by Marsden *et al.* (1980) in their studies of the adductor pollicis muscle. Since all the motor fibres supplying FDI were recruited by the supramaximal peripheral nerve stimulus, the extra force produced by cortical stimulation is likely to reflect multiple discharge of some or all of the motoneurons.

It is possible that twitch force following ulnar nerve stimulation underestimates the true twitch force of FDI. This is because ulnar stimulation activates many



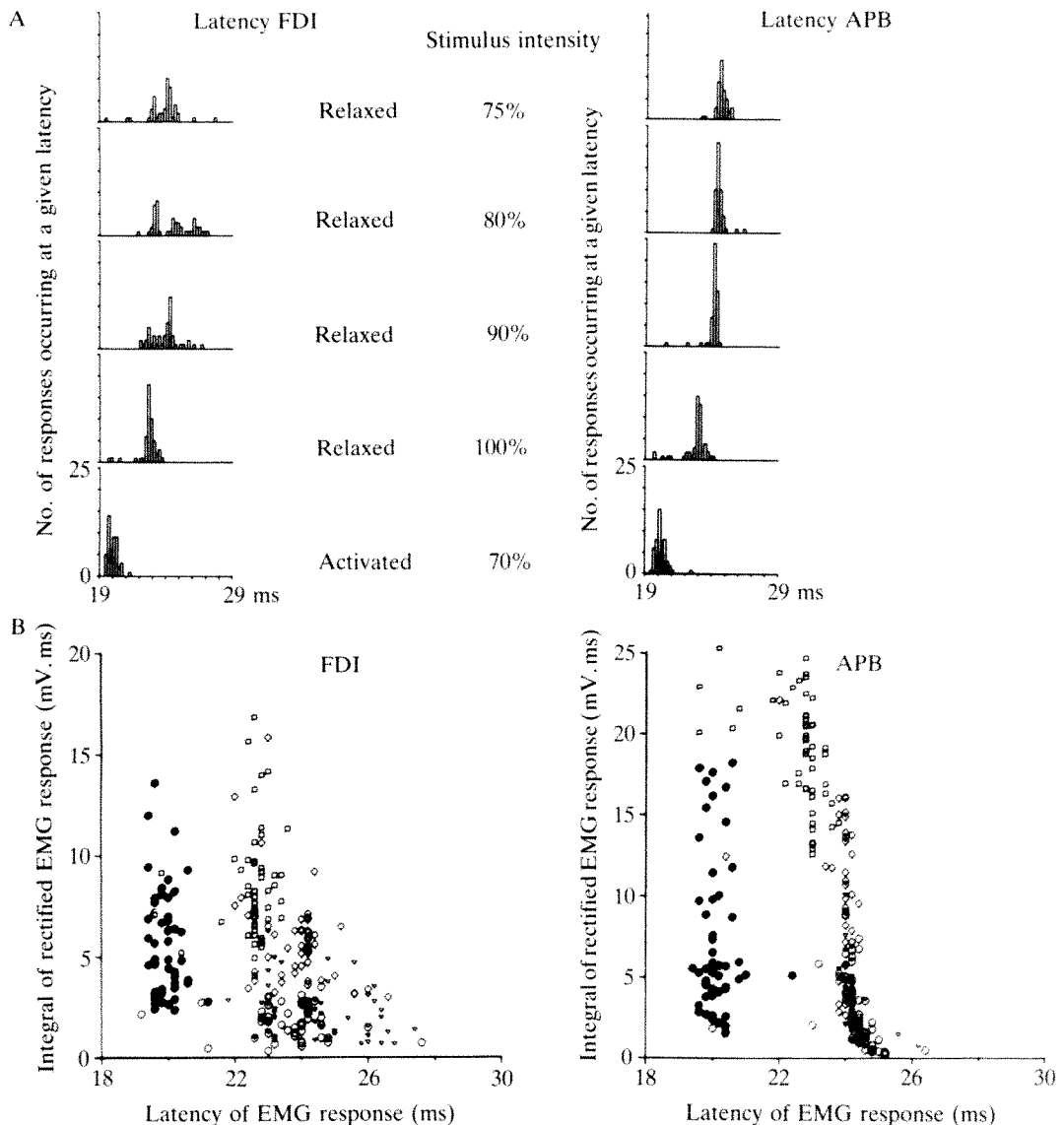


FIG. 1. Distribution of latencies to anodal cortical stimulation of EMG responses from the contralateral FDI muscle (*left panels*) and APB (*right panels*) in a single subject. A shows the frequency histogram of latencies. The top 4 histograms in each column show results obtained in relaxed muscles at four different stimulus intensities. In this and other figures the stimulus intensity is expressed as a percentage of maximum output of the stimulator. The bottom histogram shows latency distributions in active muscles (about 5% maximum voluntary effort) at a stimulus strength 70% maximum. Bin width was 0.2 ms. In B the same data have been plotted against the size of each individual EMG response, measured as the area under the rectified EMG record. Filled circles were obtained using a stimulus intensity of 70% of maximum output with the subject exerting a small background contraction of the target muscle. Open symbols were obtained with the subject relaxed and the muscles electrically silent. The stimulus intensity with the subject relaxed was 75% (circles), 80% (triangles), 90% (diamonds) and 100% (squares) of maximum output of the stimulator.

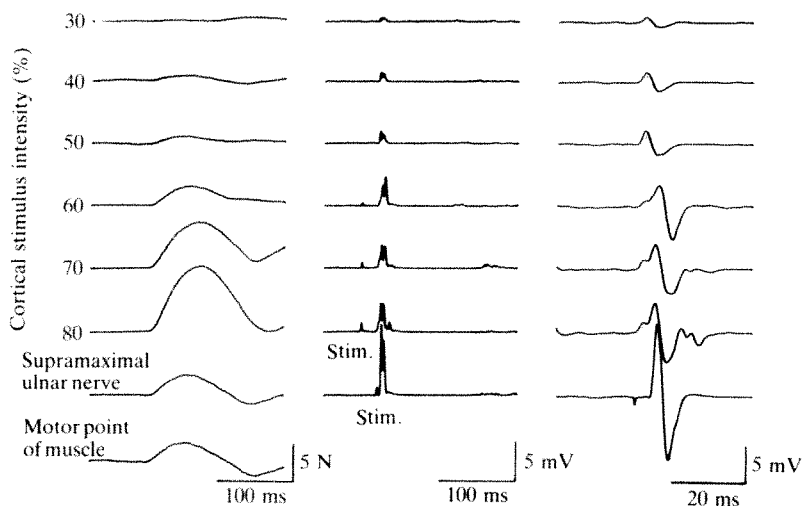


FIG. 2. Effect of increasing anodal cortical stimulus intensity on the force of twitch contraction and the EMG response from right FDI muscle. The records were obtained from a single subject exerting a 10% maximum voluntary background contraction of the muscle. The stimulus intensity is expressed as a percentage of the maximum output of the stimulator. Twitch force is shown in the *left hand* panel and surface rectified EMG in the *middle* panel. In these records the anodal cortical stimulus was applied to the opposite hemisphere 50 ms after the start of the sweep (stim.). The *right hand* panel illustrates the unrectified EMG response recorded on an expanded sweep time with the cortical stimulus given at the start of the sweep. The *bottom row* of traces were obtained by supramaximal stimulation (70 ms after start of sweep) of the ulnar nerve at the wrist. The twitch force produced by ulnar stimulation is very similar to the twitch produced by stimulation of the motor point of FDI (bottom force record: muscle). Each trace is the average of three trials. Note the increase in duration of the EMG response at stimulus intensities of 60% maximum and above. In this and subsequent figures, upwards deflection of the unrectified EMG traces represents negativity at the active electrode.

intrinsic hand muscles, some of which oppose the action of FDI, and thereby decrease the recorded twitch force. In contrast, cortical stimulation is unlikely to activate these antagonists since they will be relaxed during weak voluntary abduction of the forefinger. However, the underestimation of FDI twitch force probably is small since it is a much larger and stronger muscle than its antagonist, the first palmar interosseous. Stimulation of the FDI directly via an electrode placed over its motor point produced a force twitch very similar to that seen following ulnar nerve stimulation (fig. 2, bottom force records).

Multiple firing of motoneurons was clearly demonstrated in the collision experiment. Fig. 3 compares the EMG and force responses in FDI to stimulation of the ulnar nerve alone, cortex alone, and combined stimulation of cortex followed 10 ms later by ulnar nerve. The twitch forces produced by either cortical stimulation alone (as in fig. 2) or by combined cortical and ulnar nerve stimulation are greatly in excess of that produced by supramaximal ulnar nerve stimulation. Examination of the EMG responses on the right of the figure shows that during combined stimulation of cortex and ulnar nerve there is additional EMG activity after the ulnar M wave, in the normally silent period between M and F responses. As described in Methods, the only way activity can appear in this interval is for the cortical shock to set up repetitive firing of spinal motoneurons. The antidromic

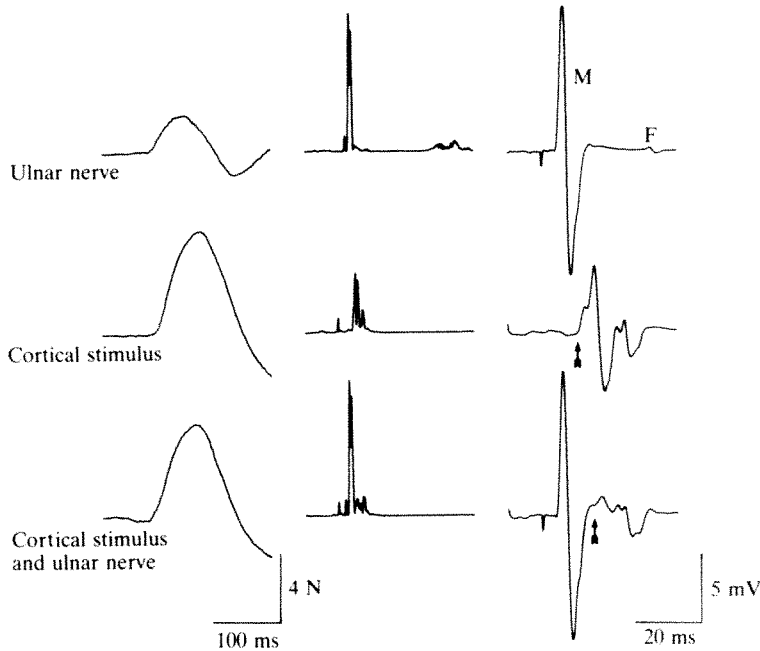


FIG. 3. Evoked isometric muscle twitches (*left column*; force records) and EMG responses (rectified, *middle column*; unrectified, *right column*) following (1) supramaximal stimulation of the ulnar nerve at the wrist to evoke a direct M wave and later small F wave (*top row*), (2) stimulation of the contralateral motor cortex at 80% maximum output (*middle row*), and (3) supramaximal stimulation of the ulnar nerve given 10 ms after a cortical stimulus (*bottom row*). Records are from one subject, made under the same conditions as in fig. 2. Each trace is the average of 3 trials. The left and middle columns were recorded on a 250 ms sweep with the cortical stimulus applied at 50 ms and ulnar nerve stimulus at 60 ms after the start of the sweep. (The reasons for choice of these timings are explained in Methods.) The unrectified EMG (right hand panel) was recorded on a 50 ms time sweep with the cortical stimulus applied at the start of the sweep. Note that when the cortical and ulnar stimuli are given together, there is additional EMG activity following the ulnar M wave, in the normally silent interval between M and F responses (compare EMG on top right). The vertical arrow on the bottom trace indicates the time at which this additional EMG activity begins. This is some 4 ms later than the onset of the EMG response to cortical stimulation given alone (arrow in the middle trace).

volley from supramaximal nerve stimulation will collide with the first orthodromic wave of cortically-evoked activity in motor axons, but later waves will continue down the same axons and activate the muscle. It is the summation of this extra activity with the maximal ulnar M wave which produces a twitch force greater than that following ulnar nerve stimulation alone. Multiple firing of motoneurons must contribute to (and may be responsible for) the prolonged duration of EMG responses at high intensities of cortical stimulation.

Fig. 3 also gives some information on the time interval between the volleys set up in motor axons by cortical stimulation. The latency of the additional EMG activity during combined stimulation is some 4 ms longer than the latency of the response to cortical stimulation applied alone (*see arrows in fig. 3*). If we assume that the onset of EMG activity to the cortical shock is produced by the first volley of motor activity, then the second volley must follow 4 ms later.

The occurrence of double or multiple firing of motoneurons depended upon two

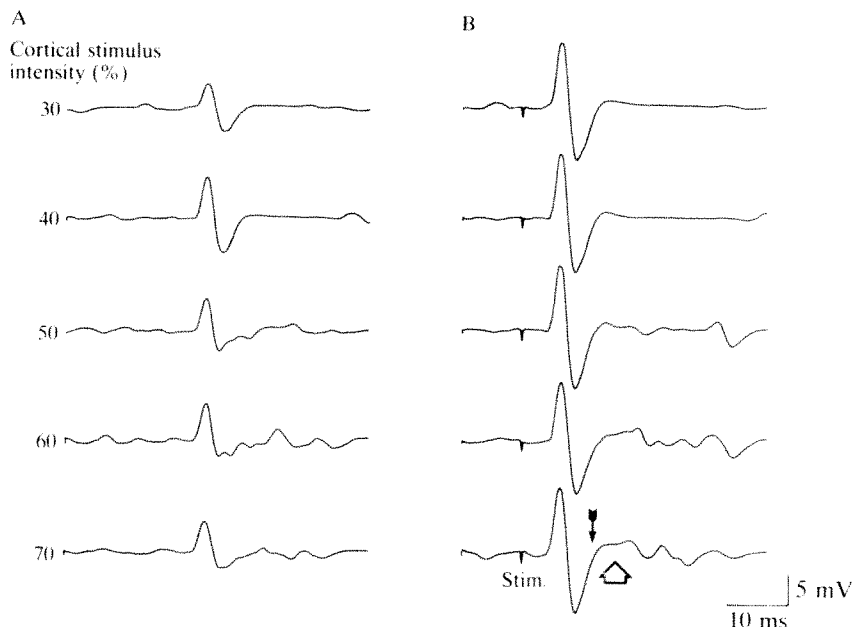


FIG. 4. Average (of three) EMG responses from the right FDI muscle of the same subject illustrated in figs 2 and 3, but with the subject exerting a 50% maximal voluntary contraction. Left hand traces (A) are responses to different intensities of anodal cortical stimuli applied at the start of the sweep. In the right hand traces (B) the same cortical stimulus was given at the start of the sweep together with a constant supramaximal ulnar nerve stimulus applied 10 ms later at the wrist (stim.); the stimulus artefact is followed by the direct M wave. Note that when the cortical stimulus was given alone, the initial EMG response appeared to be followed by later waves at shock strengths of 50% or greater of maximum output. When both stimuli were given together (*right column*), similar long-lasting EMG activity was seen at the same stimulation strengths. However, the onset of the additional later activity (thick arrow) was some 4 ms later than the expected time of onset of cortically-evoked EMG activity (thin arrow).

factors; the intensity of the cortical stimulus and the background level of voluntary activation of the muscle. Thus for the subject illustrated in figs 2 and 3, when exerting a 10% maximal voluntary contraction, multiple firing (as gauged from collision experiments similar to those shown in fig. 3) did not occur until the cortical stimulation was set to deliver a stimulus intensity of 60% of maximum output. When the same subject was studied while exerting a 50% maximal voluntary contraction, the stimulus intensity required to produce multiple firing of motoneurons was reduced to 50% of maximum output. This is illustrated in fig. 4 (again the same subject as in figs 2 and 3, but with a 50% maximum voluntary contraction). Multiple firing can be seen as the appearance of later EMG waves after the initial EMG response to cortical stimulation alone. That these waves are due to multiple firing rather than late activation of motoneurons or conduction down slowly-conducting motor axons is shown in the collision experiment of fig. 4B. Additional EMG activity occurs in the normally silent period between M and F waves at a stimulus intensity of 50% maximal.

It was not necessary for the whole of the motoneuron pool to have discharged once before multiple firing of some motoneurons occurred. This is shown for a

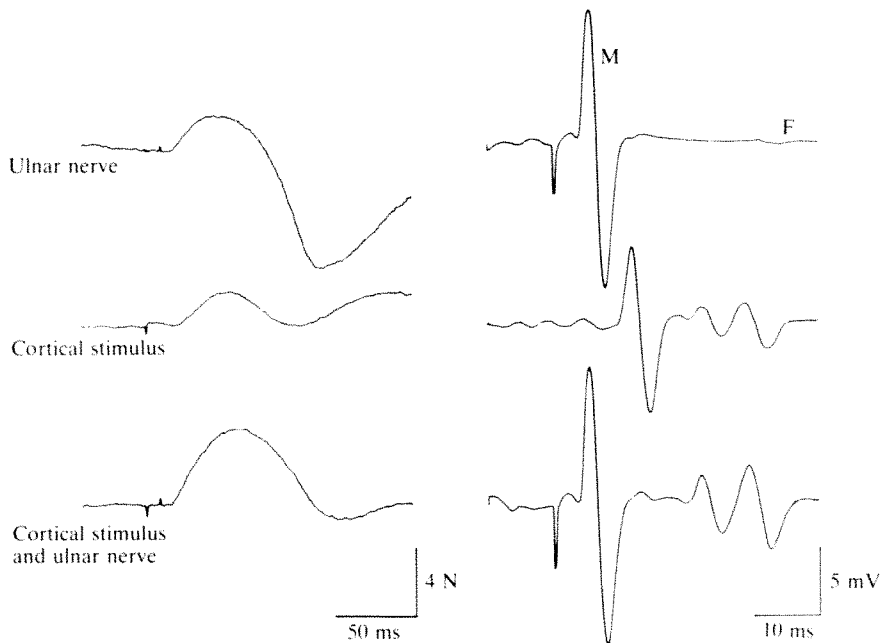


FIG. 5. Example to show that multiple firing of motoneurons can occur before the whole motoneuron pool has been recruited by a cortical stimulus. Different subject than for figs 2, 3 and 4. *Left hand* traces show muscle force recorded on a 250 ms sweep time; *right hand* traces show the EMG response from the right FDI recorded on a 50 ms sweep time. Records were obtained in a single subject under three conditions. *Top*: supramaximal stimulus to the right ulnar nerve at the wrist, delivered 50 ms (*left hand* traces) or 10 ms (*right hand* traces) after the start of the sweep. *Middle*: cortical stimulus alone delivered 40 ms (*left hand* traces) or at start of sweep (*right hand* traces). *Bottom*: cortical stimulus together with supramaximal ulnar nerve stimulus given 10 ms later. The subject exerted a 50% maximum voluntary contraction throughout and the cortical stimulator was set to deliver its maximum output. Each trace is the average of three trials. Note that the cortical stimulus alone produced force and initial EMG responses less than those generated by the ulnar nerve stimulus. However, the cortical stimulus still produced complex EMG responses which were far longer in duration than the peripheral M wave. That the later parts of the response were due to repetitive firing of motoneurons is shown in the collision test in the bottom row. With combined cortex and ulnar stimulation, there was additional EMG activity in the normally-silent period between ulnar M and F waves (compare record on top right). These later waves of activity produced a force twitch greater than that seen following supramaximal nerve stimulation.

different subject in fig. 5. Cortical stimulation alone produced a muscle twitch of submaximal force indicating that it had failed to recruit the whole motoneuron pool. Evidence for multiple firing was seen in the collision experiment from the force and EMG records (bottom traces). The EMG traces showed additional activity in the normal silent period between the FDI M and F waves. Summation of this extra activity with the M wave was responsible for the large twitch force recorded under these conditions which exceeded that produced by ulnar nerve stimulation alone.

#### *Single motor unit studies*

The existence of multiple firing in motoneurons may indicate that they receive multiple excitatory inputs. That this is the case is shown clearly by studies in single

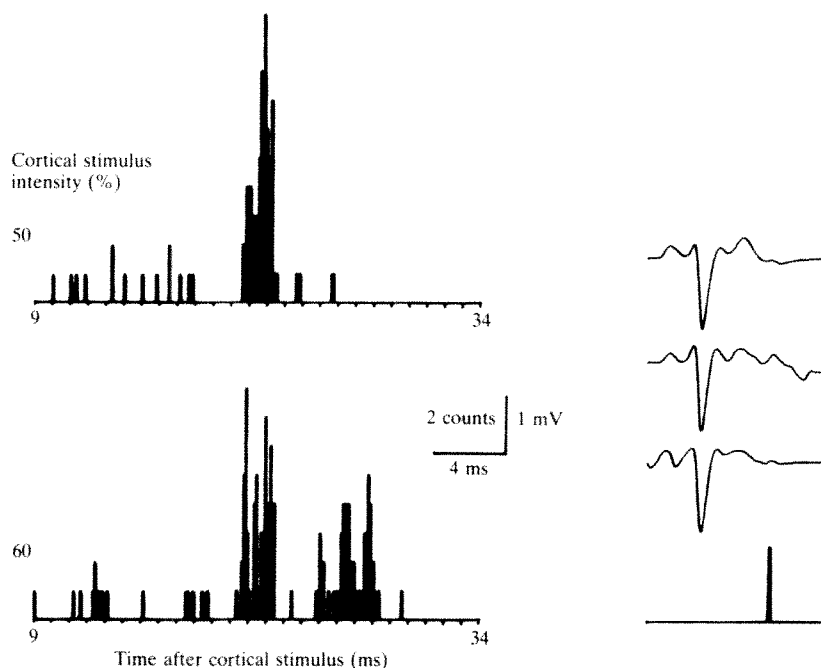


FIG. 6. Poststimulus time histograms (PSTH) (*left*) and motor unit potentials (*right*) recorded from FDI after stimulation of the contralateral motor cortex. The upper histogram was constructed following 209 stimuli at 50% maximum, the lower histogram from 197 stimuli at 60% maximum. The bin width is 0.1 ms and the traces start 9 ms after the cortical stimulus was given. The motor unit potentials on the right illustrate that no anomalous triggering of the spike discriminator occurred during construction of the lower histogram. The top potential is the average of 88 potentials recorded from the same unit in the absence of any stimulation. The middle potential is the average of 61 potentials which triggered the spike discriminator during the first peak of the lower histogram. The bottom potential is the average of the 53 potentials which triggered the spike discriminator during the period of the second peak of the histogram. All 3 potentials are similar, indicating that anomalous triggering did not occur. Additionally, during the construction of these averages it was noted that the discriminator was never triggered in *both* the first and second peak of the lower histogram. Thus, the motor unit never fired twice in response to cortical stimulation; it fired either in the first or in the second interval, or not at all. The bottom trace on the right shows the output pulse of the window discriminator, coming 6 ms after onset of the unit potential. This delay has been compensated for in the construction of the PSTHs.

motor units. The effect of a cortical stimulus on the firing probability of a single motoneuron was studied by constructing the poststimulus time histogram (PSTH) of firing of single motor units from the FDI muscle. An example is shown in fig. 6 in which PSTHs were constructed following cortical stimuli at two different strengths. At 50% maximum stimulation strength, the PSTH showed a peak of increased firing lasting for 2 ms. At 60% maximum stimulation, two broad peaks of increased firing were present, separated by 4.5 ms. It is suggested that at the higher stimulation intensity, the motoneuron received two excitatory inputs separated by 4.5 ms. This particular unit did not discharge twice in response to a single stimulus (confirmed from the tape playback of the response to each cortical stimulation). It discharged in either periods of increased firing, but never both. However, such

double excitation in other motoneurons may well have been responsible for the repetitive firing seen under the different conditions of the experiments above.

The number of stimuli averaged in these histograms was too small to allow any comment about the presence or absence of a period of inhibition before the major peaks of excitation. With a bin width of 0.1 ms, only 1 in every 5 bins are filled by averaging 200 sweeps of a motor unit discharging at 10 Hz (*see* first 8 ms of PSTHs in fig. 6). This number of sweeps was a compromise between detail in the histogram and subject discomfort; 200 or so cortical stimuli gave clear detail of excitatory peaks and yet was well tolerated by our subjects.

The results were similar in the other 6 experiments at comparable intensities of cortical stimulation. The duration of the first peak of excitation in the PSTH ranged from 1.2 to 3.0 ms (mean 1.8 ms) and at higher stimulus intensities was followed by a second peak some 4 to 5 ms later. The size of the first peak in the PSTH gives some indication of the size of the motoneuronal EPSP (Ashby and Zilm, 1982a; Fetz and Gustafsson, 1983). In all 7 experiments there was a 16 to 37% probability (mean 28%) that the motoneuron would discharge in the time defined by the first peak. The effect of stimulus intensity on the probability of firing was not investigated systematically. However, in the subject illustrated, the probabilities of firing within the first peak were similar at each intensity (31% and 37% at low and high intensities, respectively). This may imply that the size of the first EPSP had already saturated at these intensities.

*The mechanism of facilitation of the response to cortical stimulation produced by voluntary contraction*

In the previous paper we showed how voluntary contraction can increase the size and decrease the threshold of the muscle response to cortical stimulation. There are two possible, and not mutually exclusive, mechanisms for this phenomenon. First, voluntary contraction may increase spinal excitability such that a given size of descending volley may more readily excite spinal motoneurons. Secondly, voluntary contraction may increase motor cortical excitability such that a given strength of stimulus more readily excites corticospinal projections. The two options can be distinguished since if the latter is the case, then the threshold stimulus intensity required to elicit corticospinal activity should be decreased by voluntary contraction.

In order to determine the intensity at which minimal corticospinal activity occurred, we used H reflex monitoring of spinal excitability with a conditioning-test interval of  $-4.5$  ms (*see* Methods). It should be emphasized that this interval only permits examination of the effects of volleys responsible for the first peak of excitation reaching the spinal motoneurons. Fig. 7 illustrates the effect of different intensities of cortical stimulation on the size of H reflexes evoked at rest and during voluntary activity in the flexor muscles of the forearm in a single subject. At higher stimulus intensities, the H reflex was clearly facilitated in both relaxed and active conditions. Decreasing the intensity of cortical stimulation decreased the amount

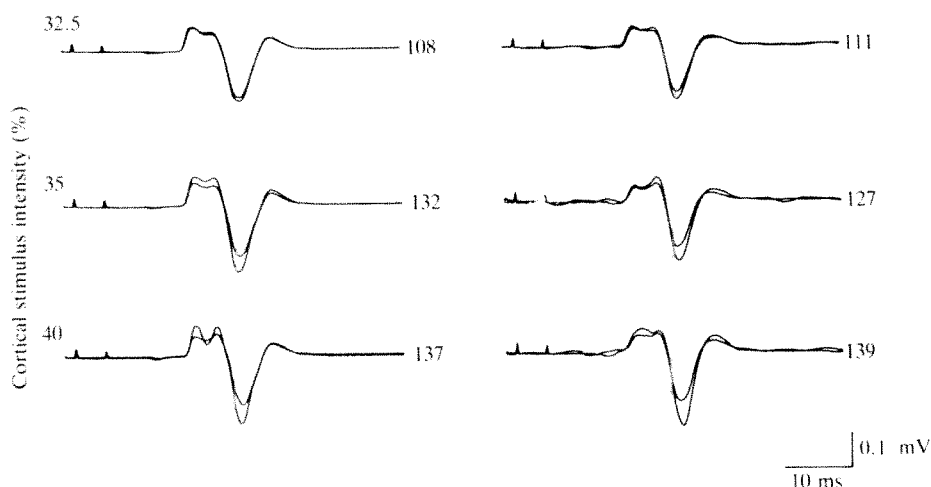


FIG. 7. Example from one subject of the effect of a voluntary contraction on the amount of facilitation of the H reflex in wrist and finger flexor muscles produced by a cortical stimulus. The median nerve stimulus (1.5 ms after the start of each trace) was applied to the elbow 4.5 ms before the conditioning cortical stimulus. It was below M wave threshold and evoked an H reflex with a latency of about 18 ms. Each record shows superimposed control and conditioned H reflexes at different cortical stimulus intensities expressed as a fraction of maximum (figures to the *left*) with the subject relaxed (*left hand* traces) and whilst exerting a small voluntary contraction (10% of maximum) (*right hand* traces). The larger H reflex in each record was that produced by the conditioning cortical stimulus. The figures to the *right* of each record indicate the amount of facilitation of the H reflex produced by the cortical stimulus. This was measured by comparing peak-to-peak amplitudes of the average response in the two conditions. Each trace is the average of 8 trials. The threshold intensity of cortical stimulation required to potentiate the H reflex was about 32.5% of maximum in this subject in both relaxed and contracting muscle. This was below the stimulus intensity required to evoke an EMG response in this subject when relaxed.

of facilitation. However the *threshold* stimulus intensity needed to produce a minimal facilitation of the H reflex (about 32.5% of the maximum in this subject) was the same for both active and relaxed condition.

Furthermore, the degree of facilitation of the H reflex at suprathreshold intensities did not change with voluntary activation of the muscle. The group data obtained in 5 subjects is shown in fig. 8, in which the cortical stimulus intensity has been expressed as a fraction of that required just to produce an effect with the subject relaxed (since the absolute threshold cortical stimulus intensity varied between subjects). Neither the threshold of the cortical stimulus required for facilitation of the H reflex nor the degree of facilitation for a given intensity of cortical stimulation changed between relaxed and active conditions. This suggests that voluntary contraction of muscle increased the size of the responses to cortical stimulation by an effect on spinal cord excitability, rather than by changing the size of the initial descending corticospinal volley.



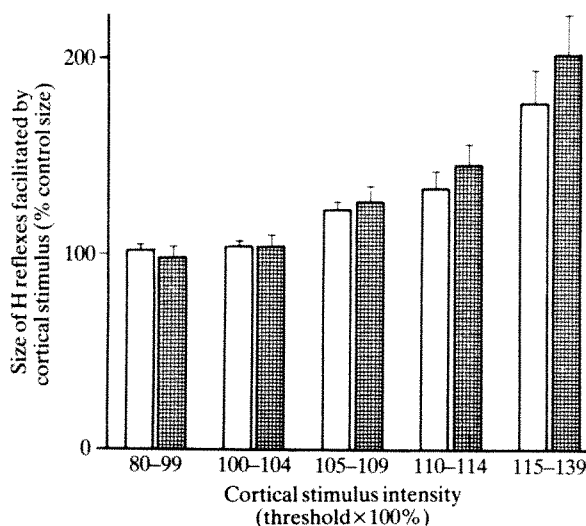


FIG. 8. Effect of voluntary contraction on threshold and degree of facilitation of the wrist and finger flexor H reflex caused by a single cortical stimulus. Mean ( $\pm 1$  SE) data from 5 subjects. H reflex size, when given in conjunction with a cortical stimulus, has been expressed as a percentage of the peak-to-peak control H reflex size. In order to normalize cortical stimulation strength between different subjects, intensity is given as a percentage of the threshold intensity needed to produce a just-identifiable facilitation of the H-reflex in relaxed individuals. Open bars were obtained with the subjects relaxed and muscles silent, and hatched bars when the muscles were activated by contraction to about 10% of maximum force.

## DISCUSSION

The latency of the EMG response to cortical stimulation depended upon a number of factors: the stimulus intensity used to evoke the response, the size of the muscle response and, most dramatic of all, voluntary preactivation of the muscle. In relaxed muscles the responses with the longest latency tended to be those with the smallest amplitude. The simplest explanation for this would be that the spinal motoneurons with the fastest peripheral conduction velocity have a higher recruitment threshold and contribute only to the larger responses (the 'size principle' (Henneman *et al.*, 1965)). Such a mechanism, however, does not explain the abrupt latency shift seen when the subject voluntarily activated the target muscle. Even EMG responses of a size similar to those evoked in relaxed muscles were shortened in latency by this manoeuvre. It is possible that a different pool of more rapidly conducting motoneurons may be recruited by the cortical stimulus during voluntary activation. However, another explanation emerged from the present results.

### *Multiple firing of spinal motoneurons*

The fact that a cortical stimulus can produce a muscle twitch that is larger than that evoked by supramaximal peripheral nerve stimulation indicates that some of the spinal motoneurons activated by the stimulus must discharge more than once. This is clearly seen in the collision experiments in which an antidromic supra-

maximal peripheral nerve volley failed to obliterate all of the descending volley generated by cortical stimulation. The latency at which EMG activity reappeared was 4 to 5 ms which represents the interval between the first and second firing of motoneurons.

The likelihood that motoneurons would fire repetitively depended on two factors: the cortical stimulus intensity and the level of voluntary muscle activation. Increasing either factor led to an increased probability of repetitive motoneuron firing. In addition, it was possible for some motoneurons to fire more than once before all the motoneurons within a pool had been recruited.

### *Interpretation of the PSTH*

That motoneurons discharge more than once in response to a single cortical stimulus suggests that the anodal cortical stimulus produced at least two periods of excitation of the motoneurons. This was confirmed by the poststimulus time histogram (PSTH) of tonically active FDI motor units in response to a cortical stimulus. The PSTH revealed at least two distinct periods of increased probability of discharge of the motor unit in response to the cortical shock. By recording postsynaptic potentials directly from cat lumbar motoneurons, Fetz and Gustafsson (1983) have shown that double excitatory postsynaptic potentials (EPSPs), separated in time by some 5 ms, gave rise to two separate peaks in the PSTH. We interpret the PSTH, therefore, as evidence that the cortical stimulus has the capacity to generate a sequence of EPSPs in the spinal motoneurons (Kernell and Wu Chien-Ping, 1967*b*). In the present results, the sequence was composed of two dominant EPSPs separated by an interval of 4.5 ms, a value which compared favourably with the estimated latency difference between the first and second firing of FDI motoneurons in the collision experiment.

If certain assumptions are made (*see* Ashby and Zilm, 1982*a*; Fetz and Gustafsson, 1983), then the shape of the first peak of the PSTH gives some indication of the shape and size of the underlying EPSP. Unfortunately, the shape of the second (and subsequent) peak in the PSTH is more difficult to interpret since it lies in the 'shadow' of decreased firing probability caused by the first peak. The average duration of the first peak in the PSTH was 1.8 ms, and is probably equivalent to the rise time of the EPSP. This is similar to the rise times of Ia facilitation in leg motoneurons calculated by Mao *et al.* (1984) using the same method. The size of the underlying EPSP can be estimated from the PSTH using the formula given by Ashby and Zilm (1982*a*):

Maximum amplitude of EPSP (units) =

$$\frac{(\text{Total counts in period of increased firing probability}) \times (\text{Mean interspike interval})}{\text{No. of stimuli}}$$

Since the motor units in the present study were held at a firing rate of approximately 10 Hz, the average EPSP amplitude is about 30 units. This means that the EPSP is capable of bringing neurons to threshold 30 ms prior to the end of the interspike interval. Similar values were quoted by Ashby and Zilm (1982*b*) for the connections of Ia afferents in the peroneal nerve to tibialis anterior when stimulated at just-submotor threshold intensity. If the maximum excursion of the membrane potential from threshold for regularly firing motoneurons of the FDI is of the order of 10 mV, as it is in cat motoneurons (Calvin, 1975), and the trajectory similar, then the initial EPSP produced by cortical stimulation would be up to 3 mV in amplitude, at least in the early-recruited units studied by the PSTH technique. These values for rise time and size are very similar to those given by Clough *et al.* (1968) in their description of the monosynaptic corticomotoneuronal projection to the alpha-motoneurons innervating the baboon's hand.

#### *Consequences of multiple excitatory inputs to spinal motoneurons*

Multiple firing of motoneurons in response to anodal cortical stimulation may explain why, with increasing stimulus intensity, the peak-to-peak size of the EMG response saturated at a value below that obtained with supramaximal peripheral nerve stimulation, although in contrast, the peak twitch force continued to grow in size and attained levels in excess of the supramaximal twitch force. Clearly, the size of the EMG response did not mirror accurately the muscle force. This can be explained, at least partially, by the fact that motoneurons may fire on arrival of the first descending volley, and/or on arrival of the second or subsequent volleys. Each firing gives rise to an EMG response. However, the waveform and interval between each EMG response may be such that the successive waves interfere thereby producing a smaller than expected peak-to-peak size. This argument can also be used to explain why, with increasing stimulus intensity, EMG waveforms become increasingly polyphasic and longer in duration.

The same hypothesis also may account for the fact that voluntary activation of a muscle led to a dramatic shortening of the latency of the EMG response. This phenomenon may be explained in the following way. A motoneuron which is excited by a sequence of EPSPs may discharge on arrival of any one of the EPSPs. Thus when the subject is relaxed, the initial EPSP may be insufficient to discharge even a small fraction of the motoneuron pool. If the stimulus intensity is increased, then the initial EPSP will increase in size and may be followed after a short interval by a second excitatory input. Although the initial EPSP may be too small to discharge motoneurons the second EPSP might summate temporally (Landgren *et al.*, 1962) with the first to discharge a fraction of the pool at a later time. The latency of the muscle response under such circumstances would be some 3 to 4 ms longer than if the motoneurons had discharged on the first EPSP. When a subject activates the muscle voluntarily, the size of the initial EPSP remains unchanged but now is likely to discharge some motoneurons because the spinal pool would

be excited by voluntary descending input. Under this condition, the latency of the muscle response would be shorter.

*Mechanisms responsible for multiple EPSPs in spinal motoneurons*

The physiological mechanisms responsible for the multiple EPSPs are not yet understood. However, we favour the idea that they were caused by the cortical stimulus setting up multiple descending volleys. The most convincing evidence for this comes from the experiments of Boyd *et al.* (1986) who were able to visualize such descending volleys in the spinal cord when they recorded from epidural electrodes during spinal surgery. At low cortical stimulus intensities a single descending volley was seen. As the stimulus intensity was increased a second descending volley appeared which followed the first with an interval of around 3 ms. Multiple descending volleys in response to a single cortical stimulus have also been observed in cat (Landau *et al.*, 1965), monkey (Patton and Amassian, 1954) and baboon (Kernell and Wu Chien-Ping, 1967*a*). In the baboon, surface anodal stimulation of the exposed motor cortex produced an initial descending volley (direct or D wave) followed by up to five further descending volleys (indirect or I waves). The D wave appeared at lower stimulus intensities than the I waves, and the various I waves themselves had different stimulus thresholds. The D wave is believed to be produced by stimulation of the axons of the large corticospinal tract neurons. The I waves, on the other hand, are believed to be caused by synaptic activation of the same corticospinal neurons through intracortical neuronal elements (Patton and Amassian, 1954; Kernell and Wu Chien-Ping, 1967*a*). By analogy, D and I waves may have been responsible for the multiple descending volleys in the present experiments.

An alternative explanation is that two descending volleys of excitation were produced by activation of two populations of corticospinal neurons with different mean conduction velocities. Two such populations of corticospinal neurons are known to exist in primates. One population consists of large diameter fast-conducting neurons and the other, which comprises about 90% of the corticospinal tract, consists of small diameter slowly-conducting neurons (DeMyer, 1959; Takahashi, 1965). In the cat, however, these conduct at velocities of  $64 \text{ m}\cdot\text{s}^{-1}$  and  $11 \text{ m}\cdot\text{s}^{-1}$  respectively (Takahashi, 1965). This difference in conduction velocities is too great to account for the small latency differences of 4 to 5 ms between arrival of successive EPSPs at cervical motoneurons.

*Possible sites at which stimulation occurs using anodal electrical stimulation of human motor cortex*

The results from our final experiment also bear on the important question of whether the technique of percutaneous motor cortex stimulation is directly comparable to surface anodal stimulation of the exposed cortex. In this experiment we were interested to know whether the threshold of the initial descending volley could be altered by the subject executing a tonic voluntary contraction of the target

muscle. Although it was not possible to measure directly the descending volley, our indirect method indicated this was not the case and that it was unaffected by a voluntary contraction. Thus the facilitatory effect of a voluntary contraction on the muscle response to a cortical stimulus is likely to occur in the spinal cord. Presumably the initial descending volley, which remains unchanged, recruits a larger number of spinal motoneurons during a voluntary contraction because they are rendered more excitable by the voluntary descending input. If the cortical neurons excited by the electrical stimulus also were involved in the execution of a voluntary contraction, then the threshold and size of the descending volley might have been expected to change by voluntary effort. The fact that this did not happen may simply mean that the stimulated neurons were not involved in the tonic voluntary contraction. Alternatively, the electrical stimulus may have excited the cortical neurons at a site which did not permit it to summate with other inputs, for example, through stimulation of the initial segment of the pyramidal neuron or its axon. This is a particularly attractive possibility since in animal experiments the D wave is believed to be produced by stimulation of the axon and not of the cell body (Landau *et al.*, 1965). These findings, therefore, are compatible with the notion that the initial descending volley produced by percutaneous stimulation of cortical neurons is analogous to the D wave produced by electrical stimulation of the exposed cortex.

In conclusion, we suggest that a single anodal cortical shock may produce multiple descending excitatory volleys which travel to the spinal cord. These may be analogous to the D and I waves recorded from pyramidal tract neurons in animal experiments. At low stimulus intensities only a D wave is produced; at higher intensities both D and I waves occur. Because of this, at high intensities, spinal motoneurons may discharge more than once and produce a mechanical muscle twitch which is greater than that seen following supramaximal peripheral nerve stimulation. In addition, the EMG response may be prolonged far in excess of normal M wave duration. If the subject is at rest, the initial D wave may be unable to discharge the motoneurons. Summation of the D with subsequent I waves may be necessary to produce a discharge. Thus the latency of EMG responses at rest may be delayed. During activation there will always be, on average, some motoneurons which are near enough to threshold to be activated by the initial D wave, and therefore the latency measured during voluntary contraction always will be short.

Such complexities of motoneuron firing in response to a single cortical stimulus must be taken into account especially when interpreting pathological data. Abnormalities of latency, size and duration of EMG responses may be explained in a number of ways and not just by alterations in the conduction velocity of central pathways.

## ACKNOWLEDGEMENTS

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## APHASIA AND NEGLECT AFTER SUBCORTICAL STROKE

### A CLINICAL/CEREBRAL PERFUSION CORRELATION STUDY

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#### SUMMARY

Sixteen patients with unilateral subcortical haemorrhagic or ischaemic stroke, confirmed by CT, were evaluated for the presence of aphasia and neglect. Compared with patients without neuropsychological deficits, left brain-damaged aphasic and right brain-damaged neglect patients showed a significantly greater reduction of cortical perfusion on N,N,N'-trimethyl-N'-[(2)-hydroxy-3-methyl-5-(I-123) iodobenzyl]-1,3-propanediamine 2 HCl I-123 (HIPDM) and single photon emission computerized tomography (SPECT). These results suggest that major cortical derangement is the crucial factor for the appearance of aphasia or neglect after a subcortical stroke. These remote effects, which are related to the size of the subcortical lesion, are interpreted in terms of interruption of neural connections (diaschisis).

#### INTRODUCTION

Aphasia may occur after ischaemic or haemorrhagic lesions involving the left thalamus or basal ganglia (*see reviews in Cappa and Vignolo, 1983; Mohr, 1983; Naeser, 1983*), while contralateral spatial neglect may be associated with damage to the same areas in the right hemisphere (*see reviews in Heilman et al., 1983; Vallar and Perani, 1987*). These disorders, however, are not an invariable correlate of subcortical damage and for a CT-assessed lesion involving these areas prediction of the presence/absence of such neuropsychological disorders appears difficult (Cappa *et al.*, 1983, 1986; Fromm *et al.*, 1985; Vallar and Perani, 1987).

Clinicoanatomical correlations relying on CT scans may, however, be misleading. Noninvasive imaging techniques for measuring regional cerebral blood flow and metabolism have demonstrated functional abnormalities in areas distant from cerebrovascular lesions and with no detectable damage on CT examination (Baron *et al.*, 1980; Lenzi *et al.*, 1982). The possibility that the occurrence of neuropsychological symptoms is dependent on an associated cortical functional derangement should then be entertained. This study aimed at correlating the



pattern of cortical perfusion, as assessed by single photon emission computerized tomography (SPECT), with the presence or absence of cognitive deficits in patients with a recent subcortical stroke.

## MATERIALS AND METHODS

### Subjects

Sixteen right-handed patients (12 males, 4 females, mean age 60.7, range 42–75 yrs) who had suffered a subcortical ischaemic or haemorrhagic stroke confirmed by CT were included in this study. All patients underwent a complete neurological examination following a standardized procedure (Bisiach *et al.*, 1983). Motor impairment and somatosensory deficits in the upper and lower limbs and visual half-field defects in the upper and lower quadrants were rated according to a four-point scale, ranging from 0 (no defect) to 3 (maximum defect). The neurological and CT scan data for each patient are summarized in Table I.

TABLE I. NEUROLOGICAL AND CT SCAN DATA

| Case | Age<br>(yrs) | Sex | Duration<br>of disease<br>(days) | Neurological defects |     |     | Nature | CT scan<br>site | Size (cm <sup>3</sup> ) | Doppler<br>sonography     | Angiography     |
|------|--------------|-----|----------------------------------|----------------------|-----|-----|--------|-----------------|-------------------------|---------------------------|-----------------|
|      |              |     |                                  | M                    | S   | VF  |        |                 |                         |                           |                 |
| 1    | 65           | M   | 13                               | 3/2                  | 1/3 | 3/3 | H      | RT              | 10.94                   | —                         | —               |
| 2    | 65           | M   | 8                                | 3/3                  | 1/1 | 0/0 | H      | LT              | 11.89                   | —                         | —               |
| 3    | 60           | M   | 5                                | 3/3                  | 3/3 | 0/0 | H      | LT pl ic, Pwm   | 15.23                   | —                         | —               |
| 4    | 71           | M   | 9                                | 3/3                  | 0/0 | 0/0 | H      | RT g/pl ic, Pwm | 15.70                   | —                         | —               |
| 5    | 49           | F   | 18                               | 3/3                  | 3/3 | 1/1 | H      | LT              | 23.80                   | —                         | —               |
| 6    | 59           | M   | 10                               | 3/3                  | 3/3 | 1/1 | H      | RT pl ic, POwm  | 33.30                   | —                         | —               |
| 7    | 47           | M   | 14                               | 0/0                  | 0/0 | 0/0 | I      | L hCN           | 8.56                    | Normal<br>R ICA occlusion | —               |
| 8    | 75           | M   | 11                               | 1/2                  | 0/0 | 0/0 | I      | R h/b CN        | 8.88                    |                           | —               |
| 9    | 70           | M   | 15                               | 0/0                  | 0/0 | 0/0 | H      | L LN            | 18.08                   |                           | —               |
| 10   | 65           | F   | 10                               | 1/1                  | 0/0 | 0/0 | H      | L LN            | 23.43                   | —                         | —               |
| 11   | 55           | M   | 1                                | 3/3                  | 0/0 | 0/0 | I      | L h/b CN, Fwm   | 34.70                   | —                         | Normal          |
| 12   | 61           | M   | 21                               | 0/0                  | 0/0 | 0/0 | I      | L Pwm           | 2.30                    | —                         | Normal          |
| 13   | 58           | F   | 23                               | 1/1                  | 0/0 | 0/0 | I      | L g ic, cr      | 3.16                    | Normal                    | —               |
| 14   | 65           | F   | 33                               | 3/2                  | 0/0 | 0/0 | I      | L Pwm           | 8.09                    | Normal                    | —               |
| 15   | 64           | M   | 24                               | 1/0                  | 0/0 | 0/0 | I      | L Pwm           | 14.59                   | —                         | Normal          |
| 16   | 42           | M   | 21                               | 0/0                  | 0/0 | 0/0 | I      | R pl ic, cr     | 53.24                   | —                         | R CCA occlusion |

R = right; L = left; H = haemorrhage; I = infarct; M = motor; S = somatosensory deficit (upper/lower limbs); VF = visual half field deficit (upper/lower quadrant); ICA = internal carotid artery; CCA = common carotid artery; T = thalamus; h/b CN = head/body caudate nucleus; LN = lentiform nucleus; cr = corona radiata; F/P/O wm = frontal/parietal/occipital periventricular white matter; g/pl ic = genu, posterior limb internal capsule.

The CT-assessed vascular lesions, 8 haemorrhages and 8 infarctions, were confined to the subcortical regions, apparently not including deep cortical areas buried in sulci such as the insula. Lesion size was measured by the method of Kertesz *et al.* (1979). Patients were investigated by SPECT, performed the same day as the CT scan assessment, while in the acute or very recent phase. The average interval between stroke onset and neuropsychological and SPECT assessments was 14.75 days (range 1–33). All patients with ischaemic lesions had Doppler sonography or conventional angiography performed on vessels appropriate to the SPECT examination. Control data for the SPECT examination were obtained from 9 normal subjects.

### Neuropsychological assessment

#### Language examination

The present aphasia examination, which was administered to the 11 patients with left subcortical

stroke, had as its first objective the detection of the presence of aphasic disturbances and, secondly, their classification according to the classical major clinical syndromes. The battery comprised a number of subtests, providing quantitative scores for the main aspects of language behaviour, including auditory verbal comprehension, oral expression, repetition, reading, and writing. The Token Test (De Renzi and Vignolo, 1962), which has proved to be an effective tool for the detection of latent receptive aphasic disorders (Boller and Vignolo, 1966), was also given. The following tests were employed.

1. *Conversational and expository speech.* The speech production tasks of Goodglass and Kaplan (1972) and the description test of Basso *et al.* (1979) were used. Speech characteristics were rated following the criteria of Goodglass and Kaplan. The type of aphasia, as reflected in the quality of speech output along the fluency/nonfluency dimension, was evaluated according to a clinical criterion, based on factors such as rate of speech, phrase length and articulatory disorders (Goodglass and Kaplan, 1972).

2. *Oral naming.* Patients were presented in succession with black-and-white pictures of 32 objects, photographed from a prototypical view, ranging from low to high frequency items, which they were required to name. If the name of an object was not given correctly within 10 s, the patient was considered to have failed on that item. One point was credited for each correct answer and the scores ranged from 0 to 32. The cut-off score, adjusted for age and educational level, computed on data from 320 control subjects (Novelli *et al.*, 1986) was 28.25.

3. *Description naming.* Patients were required to name concrete objects from verbal description. The test comprised 28 items, each of which was presented once orally. If a name for an object was not given correctly within 10 s, the subject was considered to have failed on that item. In this case, following the procedure of Coughlan and Warrington (1978), a choice of 3 items was then presented (the correct name and 2 semantically related distractors) and the patient asked to select the correct one. A second section of the test required description naming of 10 abstract items (e.g., 'fear'), with identical testing procedures. In both the concrete and abstract section of the description naming task, items ranged from high to low frequency words. In both parts of the test one point was credited if the subject produced the correct name on oral description and 0.5 points if he or she could select the appropriate choice. Scores ranged from 0 to 38. The cut-off score, adjusted for age and educational level, computed on data from 320 control subjects was 33.50 (Novelli *et al.*, 1986).

4. *Comprehension of individual words.* Patients were presented with an array of 8 black-and-white photographs, taken from a standard view, and asked to point to the item corresponding to the word spoken by the examiner. The items ranged from low to high frequency words. Four 8-item displays were presented in succession and, for each array, the examiner recited the 8 words in a random fixed order. For each stimulus word, patients were allowed 5 s to make their choice and one point was credited for each correct answer. Fifty control subjects, matched for age and educational level, had an errorless performance on this task, scoring 32 out of 32 correct answers.

5. *Token Test.* The shortened version of this sentence comprehension test was used (De Renzi and Faglioni, 1978). The cut-off score, adjusted for educational level, was 29 out of 36 correct answers.

6. *Repetition* (Bisiach *et al.*, 1983). Patients were required to repeat 12 individual letters and 22 words, differing in length, frequency, concreteness and grammatical category, spoken by the examiner. Fifty normal subjects had an errorless performance on this task (34/34 correct answers). As for sentence repetition, the Italian version (Previdi, 1975) of the Multilingual Aphasia Examination (Benton and Hamsher, 1978) was used; 21 sentences were presented by the examiner and one point was credited if the patient repeated the sentence correctly after the first presentation, while 0.5 points were given if a second presentation was needed. The average scores of 49, 42, 30 and 29 control subjects with 3–5, 6–8, 9–12 and more than 12 yrs of schooling were respectively: 17.72 (SD 2.34), 19.11 (SD 1.83), 19.48 (SD 1.59), 20.31 (SD 0.90).

7. *Auditory Forward Digit Span.* The WAIS subtest was used, but the task included also 1 and 2-

item digit strings. 150 male and 150 female control subjects had respectively a span of 6.17 (SD 0.81) and 6.01 (SD 0.84) (Grossi *et al.*, 1980).

8. *Reading*. Patients were required to read aloud 24 upper and lower case individual letters, 30 words and 10 nonwords, differing in length, frequency, concreteness and grammatical category (Bisiach *et al.*, 1983). Fifty normal subjects had an errorless performance on this task. Comprehension of individual words was assessed by a word-picture matching task (Bisiach *et al.*, 1983). Patients were presented with two displays, one with 12 written words and one with 12 black-and-white drawings of objects. They were told to identify the drawing corresponding to the word pointed to by the examiner. Fifty normal subjects had an errorless performance on this task. Finally, the patients' ability to comprehend written sentences was assessed by the 14-item Token Test in the Italian version (Previdi, 1975) of the Multilingual Aphasia Examination (Benton and Hamsher, 1978). In this visual shortened version of the Token Test, one or 0.5 points were credited respectively for correct answers within 10 s or 11–20 s (score range 0–14). The average scores of 49, 42, 30 and 29 control subjects with 3–5, 6–8, 9–12 and more than 12 yrs of schooling were respectively: 11.76 (SD 1.88), 12.56 (SD 1.24), 12.70 (SD 1.31) and 13.07 (SD 1.07).

9. *Writing* (Bisiach *et al.*, 1983). Patients were required to write their name. A written naming task was then given: patients were presented with a display of 12 drawings of objects and were asked to write the name of the objects pointed to in succession by the examiner. There were no time limits. Fifty control subjects of comparable age and educational level had an errorless performance on this task.

10. *Word fluency*. *Phonemic task*. Patients were required to pronounce as many words as they could, beginning with the letters F, P and L. S was used as an example and 1 min was allowed for each letter. *Semantic task*. This test differed from the previous one only in that three categories were used (makes of cars, fruits, animals). For either test, one point was credited for each correct word. The cut-off scores, adjusted for age and educational level, computed on data from 320 control subjects (Novelli *et al.*, 1986) were 17 and 25 words, respectively, for the phonemic and the semantic test.

### *Neglect battery*

Like aphasia assessment, the neglect examination, which was given to the 5 patients with right subcortical stroke, aimed at detecting signs of contralateral spatial neglect; it included widely used tests such as a visual exploratory task (Bisiach *et al.*, 1979) and a reading task (Colombo *et al.*, 1982) sensitive to this disorder.

1. *Cancellation task*. A white sheet of paper, 21 cm in length and 29.7 cm in width, with 13 black circles, 1 cm in diameter, was placed in front of each of the 5 patients. Each half of the sheet contained 6 circles in symmetric positions. The circle located in the centre of the sheet lay approximately in the sagittal midplane of the patient's body. Each patient was asked to cross the circles with a pencil, starting from the central one, using the ipsilateral unaffected right hand. One point was given for each left-sided omission and the score ranged from 0 (errorless performance) to 6 (no left-sided circle crossed out). Patients who omitted to cross out one or more left-sided circles were considered to show signs of contralateral spatial neglect. Control subjects had an errorless performance on this task (Bisiach *et al.*, 1984).

2. *Reading task*. Patients were given a one line full width newspaper headline, 40 cm long, and were asked to read it aloud. Ten headlines were presented, one after the other. One point was given if the patient omitted to read left-sided portions of each headline and the score ranged from 0 (errorless performance) to 10. Control subjects had an errorless performance on this task.

3. *Tactile exploratory task*. Blindfolded patients were presented with 29 wooden cubes, with sides of 1 cm<sup>2</sup>, set horizontally in a frontal plane, so that the central cube lay in the sagittal midplane of the patient's body. Patients were asked to collect all the cubes, starting from the central one, making use of the unaffected ipsilateral right hand. One point was given for each left-sided omission and the

score ranged from 0 (errorless performance) to 14. Control subjects had an errorless performance on this task and those patients who omitted to pick up left-sided cubes were considered to show signs of contralateral neglect.

4. *Anosognosia.* Anosognosia for motor impairment and for visual field defect were rated by the four-point scale of Bisiach *et al.* (1986), yielding scores ranging from 0 (no defect) to 3 (no acknowledgement of the disorder).

5. *Personal neglect.* The test of Bisiach *et al.* (1986) was used. Patients were required to touch their left hand with their right unaffected hand. Performance was rated on a four-point scale, ranging from 0 (target promptly reached) to 3 (no movement towards the target).

On the language and neglect assessments, 5 left and 3 right brain-damaged patients, respectively, showed aphasic disorders and neglect, whereas in 6 left and 2 right brain-damaged patients no signs of aphasia or neglect were found. Neuropsychological data for each patient are reported in the Appendix. All 3 neglect patients had an errorless performance in the right half-space in the cancellation, reading and tactile exploratory tasks. Three nonaphasic patients (Cases 2, 7, 13) showed a defective performance in the fluency task. Case 7, who had an ischaemic lesion of the left caudate nucleus, had defective performance on both the phonemic and the semantic subtests. Reduced word fluency has been associated with left anterior lesions and may occur without any concomitant aphasic disorder (e.g., Milner, 1964; Perret, 1974).

#### *Brain tomography*

The SPECT and I-123 HIPDM method for the assessment of regional cerebral blood flow (rCBF) has been fully described (Fazio *et al.*, 1984) and validated (Lucignani *et al.*, 1985). In this study, brain tomography started about 15 min after the intravenous injection of 7 to 8 mCi of I-123 HIPDM. In approximately 45 min of rotation time, a total head count of 4 to 5 million was recorded with a commercial rotating gamma camera on line with a dedicated computer (HP 1000). SPECT data, reconstructed and corrected for attenuation, yielded a complete set of axial tomographic slices, which were two pixels thick (centre-to-centre distance 1.2 cm) with a spatial resolution on the longitudinal and on the axial planes of 2.5 cm full width height maximum. Eight consecutive slices from the orbitomeatal line (OM) up to the vertex were obtained for each subject. In order to avoid possible artefacts due to the presence of sulci, the two slices corresponding to the vertex were excluded from the analysis. The two slices corresponding to the cerebellum (OM and 1.3 cm above) were not considered for this study. On each of the four supratentorial cerebral slices, 2.7, 3.9, 5.1, 6.3 cm above the OM line, 12 symmetric regions of interest (ROIs),  $4 \times 4$  pixels ( $2.5 \times 2.5$  cm) were considered, 6 in the left and 6 in the right hemisphere. The ROIs were located on the cortical ribbon, 2 in the anterior, 2 in the middle and 2 in the posterior region. Counts of the 2 ipsilateral anterior, middle and posterior ROIs were averaged, thus obtaining three count values (anterior, middle and posterior) for each hemisphere in each supratentorial slice.

#### *Data analysis*

A semiquantitative assessment of rCBF was performed by means of an *index of relative perfusion* between the two hemispheres, computed in 9 normal subjects from the left to right counts ratio. An overall hemisphere index value of 1.00 (SD 0.08) was found in the control group. In the 16 brain-damaged patients the index was defined as the ratio between the count values of a given ROI in the affected hemisphere and the symmetric ROI in the normal hemisphere. Index values equal/lower/higher than 1.00, respectively, indicate no interhemispheric difference, a reduction or an increase of perfusion in the damaged hemisphere. Index values ranging from 0.84 to 1.16 were considered normal.

Three index values (anterior, middle and posterior) for each of the four slices were calculated by the ratio between symmetric anterior, middle and posterior count values in the two hemispheres, yielding 12 index values for each subject. A preliminary analysis did not reveal any significant difference between left and right brain-damaged patients. These data were then used for a repeated

measurements analysis of variance, following a split-plot factorial design (Kirk, 1968). The main factors in this analysis were group (patients with/without aphasia or neglect), region (anterior, middle and posterior) and slice (four supratentorial slices).

An additional nonparametric analysis (Mann-Whitney U test) aimed at assessing whether the two groups of patients differed as to the number of index values outside the normal range ( $1.00 \pm 2$  SD).

## RESULTS

Table 2 shows the average index values of the two groups of patients. Perfusion of the damaged hemisphere in the anterior and middle regions is lower in the aphasic and neglect patients as compared with the 8 negative cases. An analysis of variance revealed significant effects of group ( $F = 11.91$ ,  $df = 1, 14$ ,  $P < 0.005$ ), of region ( $F = 22.36$ ,  $df = 2, 28$ ,  $P < 0.0001$ ) and of slice ( $F = 3.86$ ,  $df = 3, 42$ ,  $P < 0.025$ ). The group  $\times$  region interaction was significant ( $F = 4.88$ ,  $df = 2, 28$ ,  $P < 0.025$ ), whereas the group  $\times$  slice ( $F < 1$ ,  $df = 3, 42$ , n.s.), the region  $\times$  slice ( $F = 1.47$ ,  $df = 4, 84$ , n.s.) and the group  $\times$  region  $\times$  slice ( $F < 1$ ,  $df = 4, 84$ , n.s.) interactions failed to reach significance level. Tests of simple main effects showed a significant difference between the two groups of patients in the anterior ( $F = 13.20$ ,  $df = 1, 28$ ,  $P < 0.005$ ) and middle ( $F = 8.71$ ,  $df = 1, 28$ ,  $P < 0.01$ ), but not in the posterior ( $F < 1$ ,  $df = 1, 28$ , n.s.) regions. Finally, a highly significant difference of perfusion values between regions was shown in the positive group ( $F = 24.00$ ,  $df = 2, 28$ ,  $P < 0.0001$ ); such a difference was marginally significant in the negative group ( $F = 3.35$ ,  $df = 2, 28$ ,  $P < 0.05$ ).

TABLE 2. MEAN INDEX OF RELATIVE PERFUSION VALUES OF 16 PATIENTS WITH SUBCORTICAL STROKE LESIONS\*

| Region:  | Positive cases |        |           | Negative cases |        |           |
|----------|----------------|--------|-----------|----------------|--------|-----------|
|          | Anterior       | Middle | Posterior | Anterior       | Middle | Posterior |
| Slice    |                |        |           |                |        |           |
| OM + 2.7 | 0.723          | 0.802  | 1.051     | 0.923          | 0.947  | 1.043     |
| OM + 3.9 | 0.738          | 0.751  | 0.978     | 0.895          | 0.875  | 0.948     |
| OM + 5.1 | 0.748          | 0.718  | 0.966     | 0.888          | 0.855  | 0.943     |
| OM + 6.3 | 0.799          | 0.766  | 1.004     | 0.902          | 0.848  | 0.991     |

\* Eight patients showed aphasia or neglect (positive cases), 8 displayed no signs of such neuropsychological disorders (negative cases).

No index values above the normal range were found. For the number of abnormally low index values, the positive and negative groups had, respectively, mean scores of 5.87 and 1.88 out of 12 (Mann-Whitney U test,  $P < 0.01$ ), showing that the occurrence of neuropsychological disorders such as aphasia or neglect is associated with a greater extent of cortical hypoperfusion. The size of the subcortical lesion as assessed by CT (*see* Table 1) was greater in patients with aphasia or neglect as compared with patients with no evidence of such deficits (Mann-Whitney U test,  $P < 0.005$ .)

*Illustrative case reports*

*Case 3 (fig. 1).* The patient was a 60-year-old right-handed man with 8 yrs of schooling. He was admitted to hospital on December 12, 1985 a few hours after the sudden onset of loss of strength in the right limbs and difficulty in speaking. He had long-standing hypertension. On admission he showed paraphasic speech with partially preserved auditory comprehension, no visual field defects on confrontation and a right hemiplegia with increased tendon reflexes and an extensor plantar response on that side. Pain sensation was reduced on the right. On neuropsychological examination, speech output was characterized by reduced voice volume, with slight articulatory and prosodic disturbances. The patient habitually produced short sentences, with many semantic paraphasias. The frequent occurrence of word finding pauses imparted a nonfluent quality to speech output. A striking feature was the fluctuation in spontaneous speech performance: the patient alternated well-formed utterances of good communicative value with strings of neologistic jargon. Such variability of speech output has been reported previously by Mohr *et al.* (1975). Oral naming performance was partially preserved (62%); the most frequent type of error was verbal paraphasia (22%), which sometimes had a semantic relationship with the target word. Both phonemic and categorical fluency were extremely impaired. Auditory comprehension of both individual words and sentences was defective. Repetition was perfect for letters, syllables and single words; sentence repetition up to eight words was perfect. Reading aloud and reading comprehension were slightly defective, while writing was limited to his signature. In conclusion, this patient showed a mixed transcortical aphasia with several of the features which have been associated with thalamic lesions (Cappa and Vignolo, 1979; Mohr, 1983).

A CT Scan performed 5 days after onset showed a left thalamic haematoma. The SPECT study revealed a large area of hypoperfusion in the left hemisphere, extending to the cortex. Six out of 12 asymmetry indices were pathologically low.

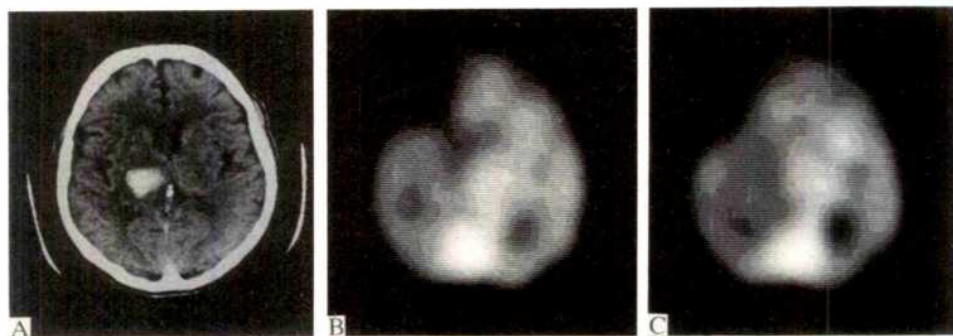


FIG. 1. *Case 3.* A, CT scan showing a haematoma involving the left thalamus and the posterior limb of the internal capsule. B, C, SPECT (OM + 3.9 and OM + 5.1) showing hypoperfusion in frontotemporoparietal cortical areas in the left hemisphere.

*Case 14 (fig. 2).* A 65-year-old right-handed woman, who suddenly developed numbness of the right side was admitted to hospital on December 27, 1984. On examination she was alert and was found to have a right facial paresis, weakness of the right arm and severe weakness of the right leg, with an extensor plantar response. Right-sided hypaesthesia and homonymous hemianopia, which cleared in a few days, were also present. The patient was unable to utter any recognizable speech sounds, but could comprehend simple commands. On neuropsychological testing on January 29, 1985, spontaneous speech was nonfluent, with associated severe impairment of articulation and melodic line. Speech output had little communicative value, consisting mainly of laboriously articulated incomprehensible phonetic sequences; occasionally single words, usually nouns, were produced. On picture naming she was severely impaired. Error analysis revealed recognizable phonemic and/or



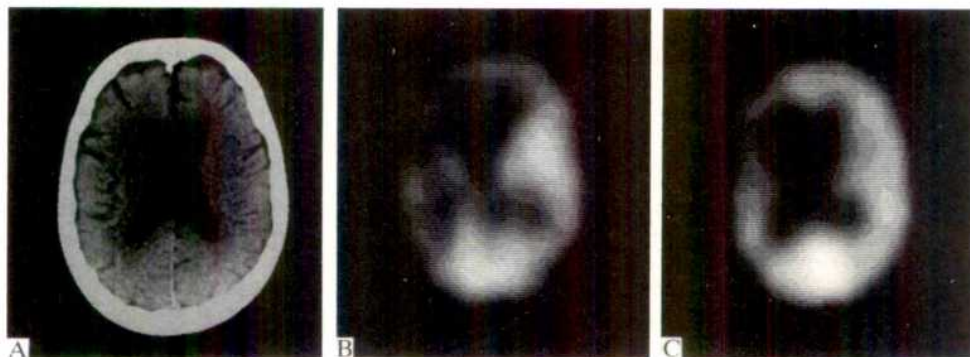


FIG. 2. Case 14. A, CT scan showing an ischaemic lesion in the paraventricular white matter in the left hemisphere. B, C, SPECT (OM + 5.1 and OM + 6.3) showing reduced perfusion in the frontoparietal cortical regions in the left hemisphere.

phonetic distortions of target words in 50% of responses; the remaining errors included neologisms (16%), which sometimes had some phonetic resemblance to target words and omissions (19%). Auditory comprehension was good on single words and moderately impaired on the Token Test (19/36). Repetition was partially preserved for letters, but grossly defective for individual words, because of the severe phonemic and phonetic impairment, also evident in spontaneous speech. Sentence repetition was impossible. As for written language, reading aloud of single letters and comprehension of individual words and short sentences, although defective, were partially preserved. In conclusion, the clinical picture of this patient can be classified as severe Broca's aphasia, with phonetic disintegration syndrome.

A CT scan performed 33 days after onset showed an ischaemic lesion in the left periventricular white matter. The SPECT study revealed a massive cortical hypoperfusion in the left hemisphere. Eight out of 12 asymmetry indices were pathologically low.

*Case 6 (fig. 3).* The patient was a 59-year-old, right-handed illiterate man. He was admitted to hospital on July 13, 1985. In the morning he had noticed a transient loss of strength in the left leg and immediately before admission, while walking in the street, he had fallen, without losing consciousness. There was a past medical history of chronic obstructive lung disease and hypertension. The patient was drowsy but rousable; the head and gaze were consistently deviated to the right. There was extinction on simultaneous bilateral visual simulation. Vertical gaze was limited. A left hemiplegia with increased tendon reflexes and left-sided anaesthesia for touch and pinprick completed

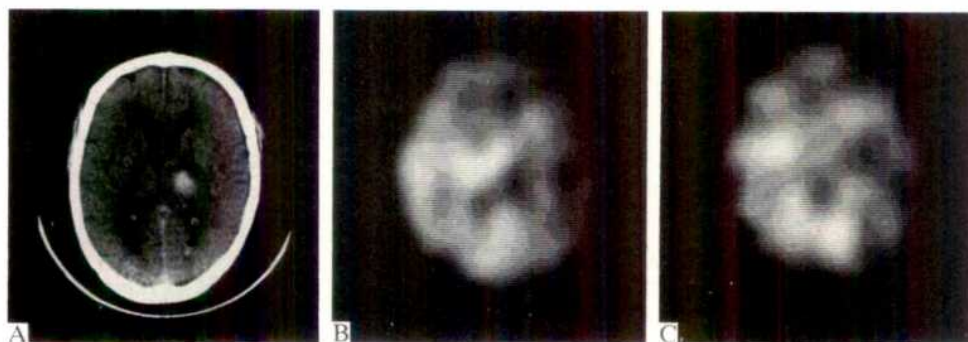


FIG. 3. Case 6. A, CT scan showing a right thalamic haematoma. B, C, SPECT (OM + 2.7 and OM + 3.9) showing a large area of hypoperfusion in the right hemisphere in frontotemporoparietal areas.

the clinical picture. On neuropsychological examination he had severe spatial neglect. In the cancellation task he did not explore the whole left half of the sheet, failing to cross out all left-sided circles even after prompting by the examiner. Conversely, he showed no signs of neglect in the tactile task. The patient was not anosognosic, although he showed mild personal neglect: when required to touch the contralateral left hand with his unaffected right hand he first touched the forearm and then reached for the target. On an auditory lateralization task (Bisiach *et al.*, 1984) he consistently displaced binaural stimuli towards the right side. The patient's level of consciousness fluctuated widely during the following few days: when alert, he was often agitated and repeatedly reported visual hallucinations localized in the right half space (gigantic spider webs on the ceiling, menacing persons approaching the bed from the right).

A right thalamic haematoma was shown by a CT scan examination performed 10 days after onset. The SPECT study revealed right hemisphere hypoperfusion extending to the cortex. Seven out of 12 asymmetry indexes were pathologically low.

### DISCUSSION

The observation of aphasia and spatial neglect after subcortical lesions raises some fundamental issues about clinicoanatomical correlation studies. Aphasia has traditionally been associated with lesions of the cortical language area (e.g., Dejerine, 1926). Interest in the anatomical correlates of spatial neglect is more recent: in this case too, however, a crucial role has been assigned to cortical areas, particularly to the right parietal cortex (Brain, 1941; Critchley, 1953). According to the classical views, the occurrence of aphasia associated with cortex-sparing lesions was usually interpreted in terms of interruption of fibre tracts connecting cortical areas. The role of subcortical grey structures, such as the thalamus and the basal ganglia, was discounted and considered to be an epiphenomenon of white matter damage (Nielsen, 1946). After the introduction of CT scanning in correlation studies, a wealth of new cases of subcortical lesions associated both with aphasia or spatial neglect has, however, been reported (for reviews, *see* Cappa and Vignolo, 1983; Vallar and Perani, 1987), arousing new interest on the issue of the role of subcortical structures in higher mental function.

Several different mechanisms have been proposed whereby in the presence of a subcortical lesion the observed clinical picture may actually reflect impaired cortical function. The most obvious explanation is based on the fact that the vast majority of the reported subcortical cases is based on CT scan localization, which may be unable to show small cortical lesions. This possibility must always be taken into account, but recent clinicoanatomical reports (Barat *et al.*, 1981; Davous *et al.*, 1984), where a complete macroscopic and microscopic examination failed to identify cortical damage in 2 patients, with respectively, basal ganglia and thalamic infarctions associated with aphasia, make this explanation not universally applicable to all cases.

The lesion may induce cortical dysfunction by mass effect due to compression, either direct or of the vascular supply. This explanation has been proposed in the case of haematomas (Mohr *et al.*, 1975; Alexander and LoVerme, 1980) and tumours (Kuroda *et al.*, 1982). However, no ischaemia due to pressure effects has



been demonstrated either in the oedematous tissue or in the cortex overlying oedema associated with cerebral tumours (Lammertsma *et al.*, 1985). Moreover, it is unlikely that the small well demarcated ischaemic lesions reported in our study and in other series (e.g., Damasio *et al.*, 1982) could by this mechanism impair cortical function.

Another hypothesis involving a vascular mechanism should be considered. In patients with acute arterial occlusions, blood flow in areas adjacent to the infarct may be sufficient for tissue viability but not for normal function ('ischaemic penumbra'; Astrup *et al.*, 1981). For occlusion of the internal carotid artery the only lesion apparent on CT scan is often a small subcortical infarction, while the cortex in the same vascular territory can be morphologically normal but hypoperfused, as shown by flow studies (Skyhøj Olsen *et al.*, 1983), and presumably hypofunctional. This mechanism presupposes the presence of an occlusion of the internal carotid artery or of the middle cerebral artery in all cases showing neuropsychological symptoms, and it is obviously not applicable to thalamic lesions, because of the different vascular supply of the thalamus and of the cortical language areas (Castaigne *et al.*, 1981). The possibility of partial ischaemic neuronal loss, the 'incomplete infarction' proposed by Lassen *et al.* (1983), has also been proposed to explain a reduction in blood flow surrounding infarcted areas. However, a sharp transition from infarcted to normal brain tissue has been shown (Nedergaard *et al.*, 1984). Finally, the observation of cortical hypometabolism after experimental subcortical lesions (London *et al.*, 1984; Girault *et al.*, 1985) can not be easily explained in terms of either 'ischaemic penumbra' or 'incomplete infarction'.

A final possible explanation of the impairment of physiological functions in unaffected brain areas is based on the concept of 'diaschisis'. This mechanism, that is, transient depression of function occurring at a distance from a focal cerebral lesion, was originally proposed by von Monakow (1914). Empirical evidence for the existence of this phenomenon was provided by Kempinsky (1958), who showed that cortical lesions in cats produce depression of electrical activity in both the ipsilateral and the contralateral hemisphere. Høedt-Rasmussen and Skyhøj (1964) demonstrated that a unilateral ischaemic stroke in humans can produce a decrease of cerebral blood flow in the contralateral hemisphere. This finding has been repeatedly confirmed by subsequent two-dimensional cerebral blood flow studies (e.g., Meyer *et al.*, 1970). The demonstration in vivo of metabolic changes in morphologically intact areas of the human brain, remote from damaged tissues, became possible only after the development of positron emission tomography. Local functional activity in the brain is directly coupled to local energy metabolism and blood flow is thus adjusted to metabolic demand in the tissue (Sokoloff, 1977). Changes in functional activity produced by sensory stimulation or deafferentation result in corresponding changes in blood flow and glucose consumption in the structures involved in the functional change (e.g., Reivich *et al.*, 1985). In cerebrovascular disease, regional cerebral blood flow and metabolism can be reduced

both in the area which appears infarcted on CT scanning and in the cortex and subcortical grey matter ipsilateral and contralateral to a supratentorial lesion, as well as at the cerebellar level (Baron *et al.*, 1980; Lenzi *et al.*, 1982).

These remote effects have been interpreted in terms of a decrease in neuronal activity caused by interruption of the input from afferent fibre pathways (Powers and Raichle, 1985). Experimental studies in the rat support the view that interruption of afferent pathways may produce remote effects. Unilateral lesions of the ventromedial globus pallidus, a major source of cortical cholinergic innervation, result in ipsilateral cortical metabolic depression (London *et al.*, 1984). Similarly, unilateral lesions of the ventromedial thalamic nucleus produce a major ipsilateral metabolic depression in the cortex and adjacent thalamic nuclei, a bilateral metabolic reduction in the basal ganglia, comparatively minor effects in the contralateral cortex (Girault *et al.*, 1985). In both hemispheres the magnitude of the remote effect was directly related to the size of the lesion. The most pronounced metabolic depression was found in ipsilateral cortical areas representing the major projection field of the ventromedial nucleus. Conversely, minor effects were shown in structures sending fibres to the ventromedial thalamic nucleus, such as the substantia nigra. The findings of Girault *et al.* (1985) suggest an anterograde effect, produced by the interruption of afferent thalamocortical pathways. In addition, the observation of metabolic depression in regions with no or few afferent connections with the ventromedial thalamic nucleus, such as the contralateral hemisphere and the basal ganglia, indicates that these remote effects are presumably not confined to the disruption of monosynaptic pathways.

The remote effects shown in the present study have been observed both in a very acute phase, such as in Case 11 examined within 24 h, and up to 30 days after stroke onset. It is unlikely that acute diaschisis reflects fully developed wallerian degeneration of fibres afferent to the cortex. Such pathological changes, however, occur over longer periods of time (*see* Duchen, 1984). In the rat, experimental thalamic lesions produce anterograde wallerian degeneration of the thalamocortical axons within 4 to 8 days (Vaz Ferreira, 1952). In a nonrecent or chronic phase, such as in the study of Baron *et al.* (1986), anterograde degeneration of afferent fibres could then deprive the cortex of subcortical input, yielding a lasting dysfunction of cortical neurons.

Interpretations of the cortical derangement associated with subcortical stroke, shown by both the present SPECT and recent PET studies (Baron *et al.*, 1986; Metter *et al.*, 1986), in terms of retrograde or transsynaptic degeneration of cortical neurons appear unlikely. In 2 aphasic patients with left putaminal-caudate (Barat *et al.*, 1981) and thalamic (Davous *et al.*, 1984) lesions, a pathological study, macroscopic and microscopic, performed months after stroke onset, did not reveal any cortical abnormality. Similarly, in an aphasic patient with a left paramedian thalamic infarction the pathological examination, performed 2 weeks after stroke onset, did not reveal cortical neuronal degeneration or loss (Bogousslavsky *et al.*, 1986). Finally, little experimental evidence is at present available, suggesting that

subcortical lesions involving the grey nuclei or the white matter can produce loss of cortical neurons by retrograde or transsynaptic degeneration (*see Baron et al.*, 1986, for references and a discussion)

The relationship between these remote effects and neuropsychological data has, however, been little investigated. For subcortical lesions, Metter *et al.* (1981, 1986) have shown cortical depression of regional cerebral blood flow and metabolism in cases of subcortical aphasia. In 8 aphasic patients with subcortical lesions, Skyhøj Olsen *et al.* (1986) found reduced blood flow in cortical areas, normal on CT scanning, by the Xe-133 intracarotid method. They interpreted the reduction in blood flow as a consequence of impaired autoregulation in areas of ischaemic penumbra and related the presence of aphasia to cortical impairment, since 5 nonaphasic patients with subcortical lesions and no evidence of arterial occlusion had normal cortical blood flow. The present SPECT finding of a reduced rCBF in cortical areas overlying deep hemisphere lesions suggests that derangement of cortical function is a crucial factor for the appearance of aphasia or neglect. An explanation of this cortical dysfunction in terms of 'ischaemic penumbra' appears unlikely since 8 of 16 patients had haemorrhagic lesions, and carotid occlusion was present in only 2 of 8 ischaemic patients. Similarly, in the aphasic group of Skyhøj Olsen *et al.* (1986), middle cerebral artery occlusion was shown in 5 infarcts, but 3 haematomas had patent vessels.

On the present results, subcortical lesions cause neuropsychological deficits when a concomitant major cortical derangement is present. This may account for the well-known finding that subcortical lesions are associated with a large number of 'negative' cases. A perusal of the literature suggests that lesions similar in site and nature may or may not be associated with the presence of neuropsychological impairments. In other words, while one can predict with reasonable accuracy from inspection of a cortical lesion on CT scan whether aphasia or neglect are present, the same does not hold true for subcortical lesions (Cappa *et al.*, 1983; Vallar and Perani, 1986). Moreover Puel *et al.* (1984) have convincingly shown that no reliable correlation can be found between the site of the subcortical lesion and the type of aphasia.

For thalamic lesions, a possible interpretation of the occurrence of negative cases can be made in terms of the intrathalamic location of the vascular damage. In the series of Graff-Radford *et al.* (1985), aphasia was associated with anterolateral infarctions, whereas patients with lateral/posterior limb of the internal capsule or posterolateral infarctions were nonaphasic or showed mild difficulties not conforming to any aphasic syndrome. Similarly, nonaphasic patients with posterior thalamic haemorrhage have been reported (Hirose *et al.*, 1985; Cappa *et al.*, 1987). Consistent with these findings, aphasic disorders have been found in patients with thalamic infarctions sparing the posterior nuclei (Archer *et al.*, 1981; Davous *et al.*, 1984; Gorelick *et al.*, 1984). These data would suggest an association between anterolateral thalamic lesions and aphasia, but language disorders have been reported to occur in patients with posterior thalamic haemorrhages (Ciemens, 1970;

Mohr *et al.*, 1975; Mazaux and Orgogozo, 1982). For right-sided thalamic lesions, a few patients with contralateral spatial neglect had vascular lesions confined to the posterior (Schott *et al.*, 1981; Hirose *et al.*, 1985) or dorsomedial (Graff-Radford *et al.*, 1985) thalamic nuclei. In the case reported by Watson *et al.* (1981), both the posterior and the dorsomedial nuclei were damaged. However, in the series of Graff-Radford *et al.* (1985), there were also patients with posterolateral lesions who did not display signs of contralateral neglect. For capsuloputamina lesions, anterior damage is typically associated with atypical nonfluent aphasias, while mild fluent aphasias can be found with posterior lesions (Cappa *et al.*, 1983; Tanridag and Kirshner, 1985). On the other hand, exceptions to this clinicoanatomical correlation pattern have been reported (Damasio *et al.*, 1982; Wallesch, 1985) and a number of patients with CT-assessed capsuloputamina lesions were not aphasic (*see* Cappa *et al.*, 1983). As for neglect, limited evidence is available but the location of the lesion within the basal ganglia does not appear to account for the presence/absence of this disorder (Vallar and Perani, 1987).

Our results have shown that it is the presence of major cortical hypoperfusion on SPECT and not the site of the structural lesion on CT, which accounts for the presence of neuropsychological symptoms. Within each specific lesion location, size is however an important factor for the appearance of major remote cortical effects leading to neuropsychological symptoms. In the present series, patients with aphasia or neglect have larger lesions than those without neuropsychological deficits. The relationship holds true both for the thalamic and the basal ganglia subgroups. In the white matter subgroup (*see* Table 1 and Appendix 1), 1 aphasic patient (Case 14) had an area of ischaemic damage smaller in size than in 1 negative case (Case 15). The magnitude of cortical derangement can then be related to lesion size, in that comparatively large lesions result in a major disruption of corticosubcortical and corticocortical connections. Consistent with this view, neuropsychological symptoms are rarely associated with lacunar lesions (Fisher, 1982), which in turn do not produce any reduction of blood flow and oxygen metabolism as assessed by PET (Rougemon *et al.*, 1983). Takano *et al.* (1985) have shown with Xe-133 that in small deep hemisphere infarctions the amount of ipsilateral cortical hypoperfusion is directly related to lesion size. In the series of Skyhøj Olsen *et al.* (1986), aphasic patients with cortical hypoperfusion had subcortical lesions larger than those found in nonaphasics with normal cortical blood flow.

The role of lesion size may nevertheless interact with the *site* of the damage. We have found neuropsychological symptoms in 4 out of 6 patients (66%) with thalamic lesions, in 2 out of 5 patients (40%) with basal ganglia lesions and in 2 out of 5 patients (40%) with damage confined to the white matter. In the series of Vallar and Perani (1986) neglect was found in 50% of thalamic lesions, in 30% of basal ganglia lesions and in only 1 out of 19 white matter lesions. All 3 patients with larger lesions involving both the thalamus and the basal ganglia had contralateral neglect. In the series of Puel *et al.* (1984) all 4 patients with thalamic lesions, 15

out of 19 patients (83%) with basal ganglia lesions and 2 out of 3 with lesions confined to the white matter were aphasic. In the series of Skyhøj Olsen *et al.* (1986) 7 out of 8 aphasic patients had lenticular lesions, while a temporal white matter lesion was shown in 1 case. Conversely, all nonaphasic patients in the study by Skyhøj Olsen *et al.* (1986) had a lesion confined to the internal capsule, with the exception of 1 case, who had a haematoma of the caudate nucleus. Finally, in the study by Baron *et al.* (1986), 8 out of 10 patients with thalamic lesions showed signs of aphasia or neglect. These findings suggest that thalamic lesions play a major role in producing neuropsychological symptoms, possibly due to the particularly extensive thalamocortical connections (Mesulam, 1985).

The present study has shown major cortical hypoperfusion in aphasic and neglect patients with a CT-confirmed subcortical lesion. Remote subcortical effects have also been reported: infarction in the territory of the middle cerebral artery often produces a subcortical dysfunction undetectable by CT scan (Kuhl *et al.*, 1980; Celesia *et al.*, 1984). Little information is, however, available as to the neuropsychological correlates of these findings. Metter *et al.* (1981) showed a metabolic reduction in both cortical and subcortical areas, unaffected on CT scan, in 4 aphasic patients with corticosubcortical lesions. In a subsequent report Metter *et al.* (1983) found comparable left thalamic and caudate metabolic depression both in patients with cortical damage and in patients with subcortical lesions. However, a major aphasic deficit was found only in the patients with cortical hypometabolism, who had a CT-confirmed lesion involving the cortex. Deuel and Collins (1984) have recently shown in the monkey that neglect after frontal lesions is associated with striatal and thalamic hypometabolism, which does not occur in recovered animals, suggesting a possible role of these structures in the restoration of function. Unfortunately, no comparable data from neglect patients are at present available.

This pattern of data indicates close corticosubcortical functional relationships, in line with views suggesting that neural systems comprising both cortical areas and subcortical structures are involved in complex cognitive functions such as language (Penfield and Roberts, 1959; Brunner *et al.*, 1982; Ojemann, 1983) and spatial attention (Mesulam, 1981; Heilman *et al.*, 1985; Rizzolatti and Camarda, 1987). The investigation of both anatomical aspects and physiological parameters in neuropsychological patients with focal cortical and deep lesions might provide further insight into the operation of these complex neural networks.

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APPENDIX 1. Neuropsychological data in left hemisphere lesions

|               | Case | OE  | ON    | DN    | AWC | ATT | L-WR | SR   | DS | R  | VWC | VTT  | WN | FWF   | CWF |
|---------------|------|-----|-------|-------|-----|-----|------|------|----|----|-----|------|----|-------|-----|
| Thalamus      | 2    | Dys | 31.25 | 31    | 30  | 30  | 34   | 10   | 6  | 62 | 12  | 11   | *  | 11    | 26  |
|               | 3    | NF  | 19.75 | 19    | 26  | 14  | 34   | 9.50 | 5  | 44 | 11  | 6.5  | 0  | 0     | 5   |
|               | 5    | NF  | 19.25 | 25.75 | 32  | 24  | 34   | 9    | 4  | 25 | 10  | 9    | 1  | 12.5  | 14  |
| Basal ganglia | 7    | NA  | 29.75 | 35    | 32  | 33  | 34   | 20   | 7  | 64 | 12  | 13.5 | 12 | 10.5  | 19  |
|               | 9    | NA  | 32    | 37    | 32  | 32  | 34   | 20   | 9  | 64 | 12  | 14   | 12 | 29.5  | 27  |
|               | 10   | F   | 31.25 | 31.50 | 30  | 24  | 33   | 13   | 4  | 60 | 12  | 7    | 0  | 0     | 19  |
| White matter  | 11   | NF  | 0     | 0     | 0   | 0   | 0    | 0    | 0  | 0  | 0   | 0    | 0  | 0     | 0   |
|               | 12   | NA  | 32    | 36.50 | 32  | 32  | 34   | 17   | 6  | 61 | 12  | 13   | 12 | 28    | 37  |
|               | 13   | NA  | 32    | 29.75 | 32  | 32  | 34   | 16   | 4  | 64 | 12  | 13   | 12 | 17.50 | 21  |
|               | 14   | NF  | 0     | 0     | 30  | 19  | 21   | 0    | 1  | 14 | 5   | 4.5  | 0  | 0     | 0   |
|               | 15   | Dys | 28.50 | 37.75 | 29  | 33  | 34   | 14   | 5  | 60 | 12  | 11   | *  | 27    | 38  |

OE=oral expression (NA=nonaphasic, F=fluent, NF=nonfluent, Dys=dysarthria); O/D/WN/=oral/description/written naming; A/VWC=auditory/visual word comprehension; A/VTT=auditory/visual Token Test; L-W/SR=letter-word/sentence repetition; DS=digit span; R=reading; F/CWF=phonemic/categorical word fluency. \*Refused.

APPENDIX 2. Neuropsychological data in right hemisphere lesions

| Case | CT | RT | TET | A | PN |
|------|----|----|-----|---|----|
| 1    | 0  | *  | 0   | 0 | 0  |
| 4    | 1  | 0  | 6   | 0 | 0  |
| 6    | 6  | *  | 0   | 0 | 1  |
| 8    | 0  | 0  | 0   | 0 | 0  |
| 16   | 0  | 3  | 14  | 0 | 0  |

CT=cancellation task; RT=reading task; TET=tactile exploratory task; A=anosognosia; PN=personal neglect. \*Illiterate.

## HEREDITARY AMYLOID POLYNEUROPATHY IN NORTH WEST IRELAND

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### SUMMARY

Seven cases of chronic sensorimotor polyneuropathy due to amyloidosis, from 7 different families, are described, in addition to the pathology in a sibling of 1 case. The age of onset ranged from 55 to 72 years. Cardiac involvement, intermittent diarrhoea and syncopal attacks were a frequent occurrence. Motor conduction velocity showed a moderate degree of slowing in 5 of 6 cases studied and marked slowing in 1. Amyloid deposits were seen in nerve biopsy material of all 8 subjects and in rectal mucosa from 1. Immunohistochemical identification revealed AF (transthyretin-derived)—amyloid in all 8 instances, confirming the presence of type 1 familial amyloid neuropathy. The genealogical data supported this analysis. Six of the 8 cases originated in a small area of the north-west coast of County Donegal in Ireland. The remaining cases also originated in the same county.

### INTRODUCTION

Polyneuropathy is a feature of hereditary amyloidosis, idiopathic amyloidosis and amyloidosis associated with malignant dysproteinaemia. Hereditary amyloid neuropathy has been classified on the basis of clinical manifestations into four types (Cohen and Rubinow, 1984). Those with onset in lower limbs have been described mainly in Portuguese (Andrade, 1952), Japanese (Araki *et al.*, 1968) and Swedish (Andersson, 1970) kinships. Those with upper limb involvement have been described in the Swiss family of Indiana (Rukavina *et al.*, 1956) and in the German family of Maryland (Mahloudji *et al.*, 1969). Lower than upper limb involvement plus nephropathy is a third type described in a family with mixed English/Scottish/Irish ancestry from Iowa (Van Allen *et al.*, 1969). Predominantly cranial nerve affection with corneal lattice dystrophy (Meretoja, 1969) are features of the fourth type.

Nonhereditary primary amyloidosis is usually characterized by the presence of immunoglobulin light chains in the serum and urine, and in the amyloid tissue (Glenner *et al.*, 1971). Hereditary amyloidosis is characterized by the presence of

a prealbumin or prealbumin-related fibril protein in the amyloid material (Costa *et al.*, 1978; Pras *et al.*, 1983; Tawara *et al.*, 1983), and in serum (Nakazato *et al.*, 1984).

Hereditary amyloid neuropathy with onset in lower limbs (Portuguese type) occurring in Portuguese immigrants has been reported from Brazil, France and Africa, and in subjects of non-Portuguese descent from the United States, Germany, Poland and Britain (Cohen and Rubinow, 1984), in addition to the well-known cases from Japan and Sweden. We first reported a cluster of 5 cases in north-west Ireland in 1983 (Dervan *et al.*, 1983) although the evidence that the condition was hereditary was circumstantial. The purpose of the present communication is to document the occurrence of hereditary amyloidosis in a cluster of 7 families in a single county, Donegal, in north-west Ireland.

### CLINICAL MATERIAL AND METHODS

Seven cases of amyloid neuropathy were seen over a period of six years. All were from County Donegal (fig. 1) and 6 cases came from a localized fifteen mile coastal strip. In addition to a clinical examination, various biochemical and radiological tests were performed to gauge the extent of systemic involvement and exclude other relevant causes of peripheral neuropathy. Five cases were male and 3 female. The age of onset ranged from 55 to 72 yrs. Six of the 7 patients have died, the duration of the illness being 5 (Case 1) 4 (Case 2) 3 (Case 3) 3 (Case 4) 3 (Case 5) and 7 (Case 6) yrs. In addition, the brother of Case 1 whose pathology is here reported, has died. Two male and 1 female patient were single.

The following indices were evaluated in all patients: blood count, biochemistry profile, erythrocyte

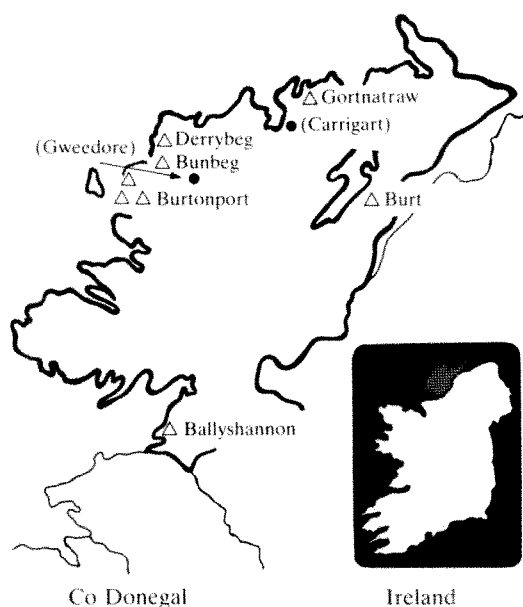


FIG. 1 Map of County Donegal showing the distribution of 8 known cases of amyloid neuropathy (open triangles).

sedimentation rate (ESR), VDRL, treponema pallidum haemagglutination, antibody screen, serum protein estimation and protein electrophoresis, urine protein electrophoresis and examination for Bence-Jones protein. Serum vitamin B<sub>12</sub> and folate were estimated in all cases except Case 2. Bone marrow was examined in 3 cases (Cases 4, 5, 7). Serum lead level was estimated in 4 cases (Cases 1, 3, 5, 6) and phytanic acid in 5 (Cases 1, 3, 4, 5, 6). Cerebrospinal fluid (CSF) was examined in 4 cases (Cases 1, 3, 4, 5). Gastrosocopy was performed in Cases 2 and 5, and sigmoidoscopy in Cases 1, 5 and 7. HLA patterns were studied in Cases 1 and 6. All patients had a chest x-ray and electrocardiogram. Echocardiography was performed in all cases except Case 6.

Electromyography and nerve conduction studies were performed in all cases except Case 3. Needle electrodes were employed for stimulating and recording in all of these cases except for 1 subject in whom surface electrodes were used.

Sural nerve biopsy was performed in all cases, and rectal biopsy in 4 (Cases 1, 3, 4, 7). Sirius red (Tribe and Perry, 1979) and Congo red (Puchtler *et al.*, 1962) stains were used on formalin-fixed paraffin sections from all patients. Adjacent sections of each were used for immunohistochemical identification of the underlying amyloid fibril protein, employing the indirect immunoperoxidase technique (Linke, 1982, 1984). The following antibodies were used: monoclonal anti-amyloid A (AA) (Linke, 1984), polyclonal antibodies against 3 different immunoglobulin lambda light chain-derived amyloids (A $\lambda$ FIS, ULI, HAR), and against a kappa chain-derived amyloid (A $\kappa$ ), polyclonal antibodies against prealbumin (transthyretin, TTR)-derived amyloid (AF) (TIE) and antibodies against TTR itself (Linke, 1982). The foregoing antibodies have been shown to categorize a large number of different amyloid syndromes on tissue sections (Linke *et al.*, 1986).

The clinical features are summarized in Table 1, EMG and conduction studies in Table 2 and electrocardiographic and echocardiographic findings in Table 3. Typical autonomic changes in 1 subject are presented in Table 4. A summary of the immunohistochemical data is presented in Table 5. One of us (R.K.), made a number of visits to Donegal and interviewed families of affected individuals, physicians and examined parish records.

TABLE 1. CLINICAL FEATURES OF 7 CASES OF FAMILIAL AMYLOID POLYNEUROPATHY

|                                      | Case       |               |           |                       |           |            |                    |
|--------------------------------------|------------|---------------|-----------|-----------------------|-----------|------------|--------------------|
|                                      | 1          | 2             | 3         | 4                     | 5         | 6          | 7                  |
| Age at onset                         | 65         | 66            | 64        | 61                    | 55        | 58         | 58                 |
| Age at diagnosis                     | 66         | 68            | 66        | 63                    | 58        | 63         | 60                 |
| Age at death                         | 70         | 72            | 67        | 64                    | 59        | 65         | —                  |
| Sex                                  | F          | M             | F         | M                     | F         | M          | M                  |
| Origin                               | Burtonport | Burtonport    | Bunbeg    | Derrybeg              | Burt      | Gortnatraw | Bunbeg             |
| Paraesthesiae                        | +          | +             | +         | +                     | +         | +          | +                  |
| Wasting                              | +          | +             | +         | +                     | +         | +          | +                  |
| Tendon reflexes                      | 0          | 0             | 0         | Absent in lower limbs | 0         | 0          | Absent ankle jerks |
| Sensory Loss                         | +          | 0             | +         | +                     | +         | +          | +                  |
| Postural hypotension                 | +          | +             | +         | 0                     | +         | 0          | 0                  |
| GI tract                             | Diarrhoea  | Gastric ulcer | Diarrhoea | 0                     | Diarrhoea | Diarrhoea  | 0                  |
| Cardiac involvement                  | +          | +             | +         | +                     | +         | +          | +                  |
| Nerve biopsy (amyloid stain)         | +          | +             | +         | +                     | +         | +          | +                  |
| Myelinated fibre count* <sup>2</sup> | 32         | 2785          | 90        | 470                   | 253       | 20         | ND                 |
| Rectal biopsy                        | +          | ND            | 0         | 0                     | ND        | ND         | +                  |

\* Density of myelinated fibres/mm<sup>2</sup>. ND = not done.

TABLE 2. EMG AND NERVE CONDUCTION STUDIES IN 6 CASES OF FAMILIAL AMYLOID POLYNEUROPATHY

| Case | Age (yrs) | Motor                                                           | Sensory                        | EMG                    |
|------|-----------|-----------------------------------------------------------------|--------------------------------|------------------------|
| 1    | 66        | Peroneal: 37 m·s <sup>-1</sup>                                  | Sural* and median: no response | Widespread denervation |
| 2    | 68        | Peroneal: no response in<br>EDB**; ulnar 24.5 m·s <sup>-1</sup> | Median and ulnar: no response  | Widespread denervation |
| 4    | 63        | Peroneal: 4 m·s <sup>-1</sup> **                                | Not studied—poor cooperation   | Widespread denervation |
| 5    | 58        | Ulnar: 38 m·s <sup>-1</sup>                                     | Median and ulnar: no response  | Widespread denervation |
| 6    | 63        | Peroneal: no response in<br>EDB**; ulnar 48 m·s <sup>-1</sup>   | Median: no response            | Widespread denervation |
| 7    | 60        | Peroneal: 26 m·s <sup>-1</sup> ; ulnar<br>48 m·s <sup>-1</sup>  | Sural and ulnar: no response   | Widespread denervation |

\* Needle electrodes used for stimulation and recording. \*\* This patient had over 95% reduction in myelinated fibres in the sural nerve with abnormally segmented myelin in residual fibres. EDB = extensor digitorum brevis.

## CASE REPORTS

### Case 1

A 66-yr-old Burtonport (fig. 1) housewife presented with frequent syncopal attacks of six months duration. She also complained of paraesthesiae and weakness in all four limbs and intermittent diarrhoea of similar duration. She had marked postural hypotension (lying BP 140/90 mmHg; standing BP 95/50 mmHg). Further autonomic studies supported the diagnosis of an autonomic neuropathy (*see below*). Neurological examination revealed marked wasting and weakness in all muscle groups, with absent tendon reflexes and flexor plantar responses. A distal sensory loss to touch and pin-prick was present in upper and lower limbs. Temperature sensation was impaired in the legs as was joint position and vibration sense. CSF protein was 0.6 g/l. Chest x-ray revealed an increase in heart size and small bilateral pleural effusions. EMG and conduction studies confirmed the presence of a generalized sensorimotor neuropathy (Table 2). ECG and echocardiography suggested the presence of a cardiomyopathy (Table 3). Amyloid deposits were found in both sural nerve and rectum. Immunohistochemical examination revealed this to be of AF, or familial type (Table 5). Her disease progressed over four subsequent years, and she died at the age of 70 yrs in cardiac failure.

*Family history.* Her father had died at 66 yrs, before which he had had difficulty in walking and

TABLE 3. ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY FINDINGS IN 7 CASES OF FAMILIAL AMYLOID POLYNEUROPATHY

| Case | Electrocardiography                                                                                   | Echocardiography |        |
|------|-------------------------------------------------------------------------------------------------------|------------------|--------|
| 1    | Prominent Q waves in V1, V2, V3; first degree heart block. LBBB; occasional ventricular escape beats. | PLV wall*        | 2.5 cm |
|      |                                                                                                       | IVS              | 1.5 cm |
| 2    | Pacemaker in situ (complete heart block)                                                              | PLV wall         | 2.0 cm |
|      |                                                                                                       | IVS              | 1.5 cm |
| 3    | Prominent Q waves in II, III, AVF; RBBB; first degree heart block                                     | PLV wall         | 1.4 cm |
|      |                                                                                                       | IVS              | 1.2 cm |
| 4    | Prominent Q waves in II, III, AVF, V1, V2, V3; intermittent atrial fibrillation.                      | IVS              | 1.3 cm |
| 5    | Prominent Q waves in II, III, AVF; intermittent atrial fibrillation.                                  | PLV wall         | 2.0 cm |
|      |                                                                                                       | IVS              | 1.2 cm |
| 6    | Prominent Q waves in II, III, AVF V1, V2, V3; atrial fibrillation                                     | Not done         |        |
| 7    | Prominent Q waves in II, III, AVF; first degree heart block.                                          | IVS              | 1.0 cm |

LBBB = left bundle branch block; RBBB = right bundle branch block, PLV = posterior left ventricular wall, normal 0.8–1.1 cm. IVS = interventricular septum, normal 0.7–1.2 cm.

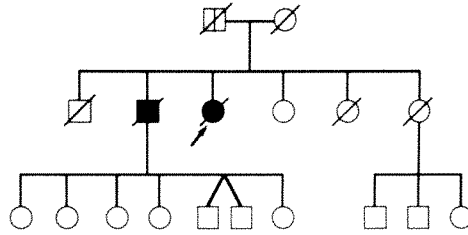


FIG. 2. Pedigree for *Case 1* showing 2 affected siblings (filled symbols) and probably affected father (vertical line in symbol). Proband indicated by arrow; oblique lined through symbol = dead.

used a stick. Her mother had died at 91 yrs of 'old age'. One brother was subsequently found to have a peripheral neuropathy in whom sural nerve biopsy material was established by us as being positive with Sirius red stain and typed as AF type (see fig. 2). Another brother died at 21 yrs of tuberculosis. Of her 3 sisters, 1 remains alive and well. The other 2 died at 21 and 26 years, respectively. The patient had no children. Her affected brother had a family of 7 children, all still alive and currently ranging in age from 23 to 33 yrs (see fig. 2). The affected siblings' mother and the mother of Case 2 were second cousins.

#### Case 2

A 68-yr-old Burtonport farmer complained of palpitations, exertional dyspnoea and two episodes of unconsciousness in the preceding two years. On investigation elsewhere he was found to have complete heart block and had a cardiac pacemaker inserted. He also complained of progressive weakness in hands and feet of one year's duration and numbness in his lower limbs of four months' duration. He had postural hypertension (lying BP 130/90 mmHg; standing BP 90/70 mmHg). There was distal weakness in upper and lower limbs and absent tendon reflexes. No sensory deficit was demonstrable clinically. No sweating was detected in his limbs following elevation of his central body temperature by 3° C. ESR was 40 mm in 1 h but serum protein electrophoresis was normal. EMG and nerve conduction studies confirmed the presence of a generalized sensorimotor neuropathy (Table 2). Echocardiography suggested the presence of cardiomyopathy (Table 3). Amyloid deposits were detected in the sural nerve. This was shown to be of AF type (Table 5). In the course of his illness he developed a benign gastric ulcer confirmed on gastroscopy. He died of cardiac failure at 72 yrs.

*Family history.* His father had died at 83 yrs of a 'stroke'. His mother had died at 60 yrs of unknown cause and a history of the nature of this illness proved unobtainable. She was a second cousin of the mother of Case 1. The patient had 7 brothers and 5 sisters, of whom 1 sister survives and is well at 79 yrs in the United States. One sister died at 62 yrs of 'multiple sclerosis'. One nephew died at 32 yrs of multiple sclerosis, diagnosed in the US Air Force. The patient was unmarried.

#### Case 3

A 66-yr-old woman from Bunbeg presented with weakness and paraesthesiae in the lower limbs of two years' duration and in the lower limbs of one year's duration. She complained of syncopal attacks over the two-year period. She had been investigated for intermittent diarrhoea of similar duration. She had postural hypotension (lying BP 110/70 mmHg; standing BP 80/40 mmHg). There was severe wasting of both thenar eminences and quadriceps in addition to less severe generalized muscle wasting. Tendon reflexes were absent. Distal sensory loss to superficial sensation was present in all limbs and there was impairment in joint position and vibration sense. CSF protein was 0.8 g/l. ECG and echocardiography suggested the presence of a cardiomyopathy (Table 2). Amyloid deposits were found in the sural nerve; this was of AF type (Table 5). In the course of her illness she developed severe painless burns in both legs. She died of congestive cardiac failure at 66 yrs.

*Family history.* She was illegitimate and never knew her father. Her mother died at 75 yrs of a presumed stroke. She had 1 maternal aunt who died at roughly the same age as her mother. She had no known siblings and was herself unmarried.

#### Case 4

A 63-yr-old single retired farmer from Derrybeg presented with burning pain in the lower and upper limbs and unsteadiness of gait, all of about 18 months' duration. He had wasting and weakness of all limb musculature, especially in the lower limbs. Tendon reflexes were absent in the legs, though present in the arms. Distal sensory loss for superficial sensation was present in all limbs. Joint position and vibration sense were impaired in the feet. There was clinical evidence of cardiac enlargement. CSF protein was 0.4 g/l. EMG and nerve conduction studies showed evidence of a generalized sensorimotor neuropathy with marked motor slowing (*see* Table 2 and appended comment on pathology). ECG and echocardiography suggested the presence of cardiomyopathy (Table 3). The sural nerve revealed amyloid deposits, although rectal biopsy was negative. The amyloid was of AF type (Table 5). He died at 64 yrs of 'general inanition'.

*Family history.* His father had died of cancer at 68 yrs. His mother had died suddenly of uncertain cause at 30 yrs, during pregnancy. He had 4 sisters, of whom 1 died at 58 yrs having had leg symptoms ('rheumatic') for 18 years, being invalided for the 7 years before her death, with pains and weakness in all limbs associated with urinary and faecal incontinence. Two sisters had died in childhood and 1 sister was alive and well. Two of his 3 brothers had died at the respective ages of 57 and 54 yrs of heart attacks, and the third was alive and well.

#### Case 5

A 58-yr-old retired nurse from Burt had a two-year history of syncopal attacks and progressive weakness and paraesthesiae in all four limbs. She had burned her hands and developed blisters without noting pain. During the course of her illness she had developed intermittent diarrhoea. She had postural hypotension (lying BP 100/70 mmHg; standing BP 70/50 mmHg). There was severe wasting and weakness of proximal and distal muscles. Distal sensory loss to superficial sensation was present and she had impaired joint position and vibration sense. Tendon reflexes were absent. CSF protein was 0.75 g/l. EMG and nerve conduction studies confirmed the presence of a generalized sensorimotor neuropathy (Table 2). ECG and echocardiography suggested the presence of a cardiomyopathy (Table 3). Amyloid deposits were found in the sural nerve and were of AF type (Table 5). She died at 59 yrs of heart failure.

*Family history.* Her father died at 69 yrs of heart failure. Her mother had died at 45 yrs of post-partum haemorrhage. However, her mother in turn had been bed-ridden for two years before death and the patient maintained that her own illness resembled hers (*see* fig. 3). This maternal grandmother originated from Gweedore (fig. 1). The patient had 4 brothers and 8 sisters, all younger than her and in good health. She had 3 children ranging from 13 to 23 yrs.

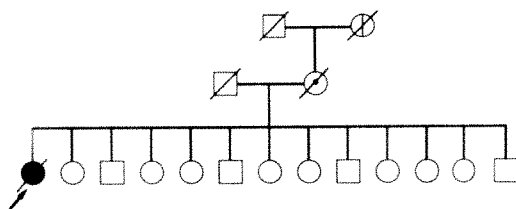


FIG. 3. Pedigree for Case 5 illustrating a possible line of transmission obscured by the early death of the proband's mother, who died aged 45 yrs from post-partum haemorrhage. Her mother was bedridden for two years before her death from an illness similar to that of the proband. Symbols as in fig. 2.



*Case 6*

A 63-yr-old retired farmer from Gortnatraw presented with a five-year history of pins and needles and a two-year history of progressive weakness in his legs. Similar complaints were noted subsequently in his upper limbs. He had had intermittent diarrhoea for the preceding three years. Blood pressure was 110 mmHg without postural drop. There was severe wasting and weakness in all muscle groups. Tendon reflexes were absent. Distal sensory loss for superficial sensation was present in all limbs. Joint position and vibration sense were impaired. A low serum vitamin B<sub>12</sub> (190 nanograms%) had been noted and he had been treated with parenteral vitamin B<sub>12</sub> without benefit. His Schilling test was subsequently normal. Anti-nuclear antibodies were detected in his serum. EMG and nerve conduction studies confirmed the presence of a generalized sensorimotor neuropathy (Table 2). ECG showed changes consistent with a cardiomyopathy (Table 3). Amyloid deposits were found in the sural nerve and these were of AF type (Table 5).

*Family history.* His father died at 64 yrs. He had used a stick for 3 yrs and had been bed-ridden for 6 months before death (see Fig. 4). His mother had died at 62 yrs of a 'stroke' and had chronic renal disease. His paternal grandfather died at 60 yrs of uncertain cause, thought to be carcinoma of the stomach, and his grandmother at 72 yrs of 'cardiac failure'. No history was obtainable relating to his maternal great grandparents. On the paternal side, his great grandfather died at 60 yrs of 'cardiac failure', having been ill for one year. One of the patient's 6 sisters died at 39 yrs of 'heart trouble', 1 at the age of 15 yrs and a third in childhood. One sister had 'arthritis' and 2 were alive and well. He had no brothers.

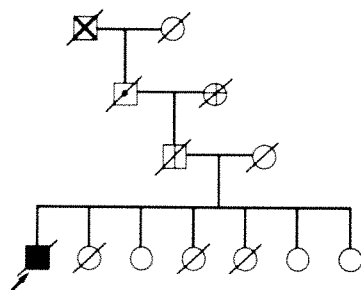


FIG. 4. Family of Case 6 showing possible transmission from the proband's father, with uncertainty entering beyond that point. His father (vertical line through symbol) died at 64 yrs following a similar illness; the father of this individual (dot in symbol) died at 60 yrs of unknown causes; his father (cross in symbol) died at 72 yrs from cardiac failure.

*Case 7*

A 60-yr-old maintenance worker presented with a two-year history of progressive numbness and weakness in arms and legs, weight loss of 13 kg and impotence. Blood pressure was low (lying BP 114/66 mmHg; standing BP 110/68 mmHg). He had generalized wasting and weakness in arms and legs, with fasciculations in the arms. Tendon reflexes were absent. There was distal sensory impairment for light touch with hyperalgesia to pin-prick in the same distribution. Vibration sense was absent below the costal margin but joint position sense was intact. EMG and nerve conduction studies confirmed the presence of generalized sensorimotor neuropathy (Table 2). ECG and echocardiography were suggestive of a cardiomyopathy (Table 3). Amyloid deposits were found in the sural nerve and rectum and these were of AF type. Liver biopsy revealed an unexplained granulomatous hepatitis.

*Family history.* One of his 3 brothers died at 49 yrs of renal disease. Two are alive and well at 58 and 54 yrs. His one sister had 'arthritis' but is not in any way incapacitated. His mother died at 66

yr of 'cardiac failure', but there is no such history in her siblings. There is no positive history of such illness in any of his grandparents. He has 3 children.

## OBSERVATIONS

### *HLA typing*

This was studied in 2 cases and was as follows. Case 1: A11, A28, B27, Bw35, DR2; Case 6: A3, A19, B7, B.12, DR2.

### *Autonomic studies*

Five of the 7 subjects had postural hypotension, marked in 4 (*see Case Reports*). The resting blood pressure was low in the other 2 subjects (average systolic pressure 110 mmHg in each case). However, the presence of a cardiomyopathy necessitates caution in the interpretation of the latter. Similarly, caution is required in the interpretation of responsiveness of cardiac rate to various stimuli. One subject had complete heart block (Case 2) and a pacemaker in situ, and 2 others had atrial fibrillation at the time of examination (Cases 4, 6), invalidating such an approach. All the others had a conduction disturbance of some type (*see Table 3*) which nevertheless would not necessarily invalidate the results. Heart rate (R-R interval) and blood pressure were recorded under different conditions, including changes in posture (2 cases with heart rate and all cases with blood pressure), Valsalva manoeuvre and variations in breathing in 4 cases (Cases 1, 3, 5, 7) and cold pressor test, mental arithmetic and intravenous atropine in 3 cases (Cases 1, 3, 5). In all such instances there was little beat-to-beat variation in rate. Table 4 illustrates a typical set of such results (Case 3).

TABLE 4. PULSE RATE AND BLOOD PRESSURE UNDER VARYING CONDITIONS IN A CASE OF FAMILIAL AMYLOID POLYNEUROPATHY

|                        | Heart rate* |        |       | Blood pressure (mmHg) |        |        |
|------------------------|-------------|--------|-------|-----------------------|--------|--------|
|                        | Before      | During | After | Before                | During | After  |
| Posture                |             |        |       |                       |        |        |
| Lying                  |             | 64     |       |                       | 120/85 |        |
| Sitting                |             | 64     |       |                       | 96/74  |        |
|                        | 64          | 64     | 64    | 130/90                | 100/70 | 120/80 |
| Hyperventilation       | 64          | 63     | 64    | 130/90                |        | 115/80 |
| Mental arithmetic      | 63          | 63     | 64    | 125/90                |        | 120/90 |
| Cold                   | 64          | 63     | 63    | 120/90                |        | 125/90 |
| Atropine (1.2 mg i.v.) | 64          | 64     | 64    | 120/85                | 130/90 | 130/90 |

\* Calculated on R-R interval.

### *Pathology*

Amyloid material was detected in the sural nerve in all 7 patients and in the specimen from the brother of Case 1 (fig. 2). The extent of deposition varied from patient to patient. The smallest deposits were located in the endoneurium, often

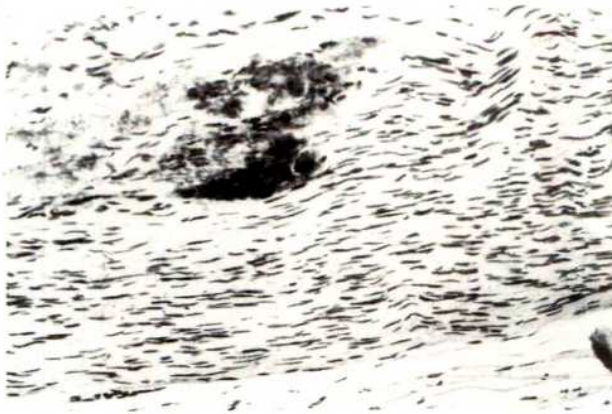


FIG. 5. Longitudinal section of sural nerve from Case 4 showing large endoneurial amyloid deposit (sirius red  $\times 250$ ).

involving very small endoneurial vessels. Some patients showed extensive deposition (fig. 5). Such patients showed epineurial deposits in addition. Rectal biopsy was positive in 2 of the 4 cases studied. A muscle biopsy from Case 5 showed denervation atrophy with extensive amyloid deposition in the perimysium and adherent adipose tissue. Myelinated fibres were counted in cross sections of osmicated paraffin-embedded nerve in 7 of the 8 specimens of biopsy obtained material. Counts were carried out using an eyepiece graticule and expressed as total myelinated fibres/mm.<sup>2</sup> Sural nerve specimens from all 7 cases showed extensive loss of myelinated fibres with counts ranging from 20 to 3356/mm<sup>2</sup> (mean 1000/mm<sup>2</sup>). Table 4 indicates the individual counts. Normal average mean count in paraffin-embedded, formalin-fixed sections for the sixth decade is 11200/mm<sup>2</sup> (Tohgi *et al.*, 1977).

*Immunohistochemical typing* (Table 5). The amyloid deposits of all 8 sural nerve biopsy specimens showed strongest binding of the antibodies directed against AF-amyloid fibril protein which is derived from transthyretin (TTR), and against TTR itself. The other antisera showed marginal reactions only, these reactions being due to cross reactions of anti-AL antibodies with immunoglobulins in the amyloid deposits. No reactions were observed with monoclonal anti-AA. Fig. 6 illustrates such findings in adjacent sections (Case 6). Thus all 7 cases and the brother of Case 1 belong to the familial type 1 polyneuropathic AF-amyloid group.

#### *Genetic aspects*

The establishment on clinical/epidemiological grounds alone of the familial nature of this condition would have proven difficult. The disease is of quite late onset, occurring in an area where early death and uncertain cause of death was common for the generations under study and from which there has been a steady high rate of emigration. The county is isolated, without visiting neurologists and

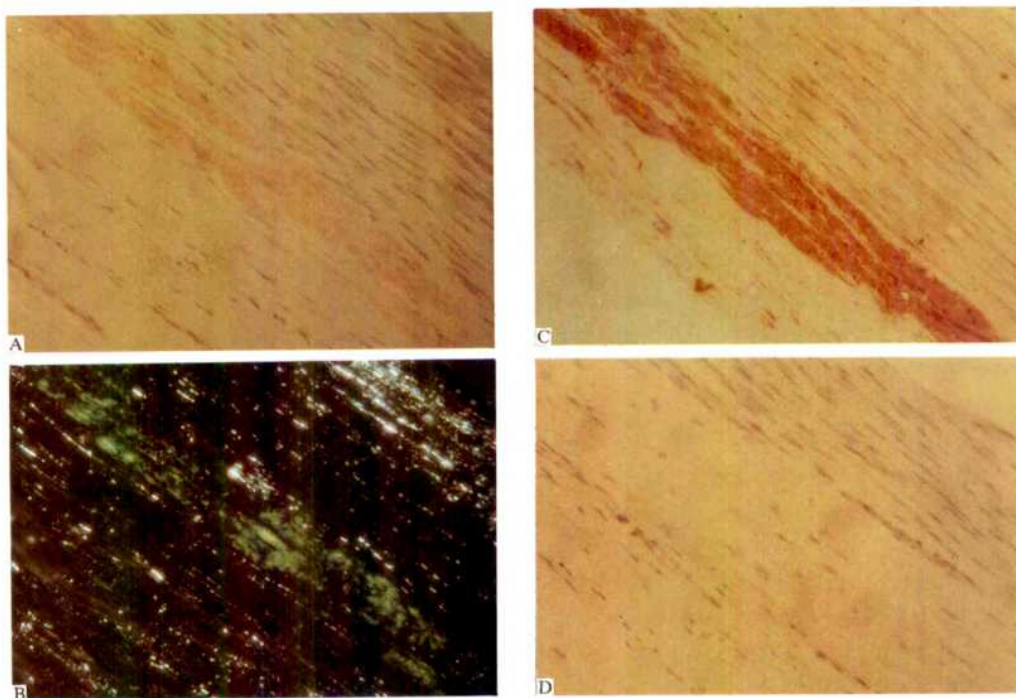


FIG. 6. Amyloid neuropathy in *Case 6*. Immunohistochemical identification of amyloid on sural nerve biopsy. A, paraffin section stained with Congo red according to Puchtler *et al.* (1962). Amyloid is pink-coloured. B, same section as A in polarized light; green birefringence identifies amyloid. C, adjacent section exposed to antiserum against AF (TIE) using the indirect immunoperoxidase method; positive reaction indicated by red-brown colour. D, adjacent section exposed to anti-AA showing no reaction. All  $\times 200$ .

TABLE 5. IMMUNOHISTOCHEMICAL TYPING OF AMYLOID DEPOSITS IN NERVE BIOPSIES OF PATIENTS WITH FAMILIAL POLYNEUROPATHY

| Case | Amount of amyloid* | Immunohistochemical reaction with antiserum against** |             |            |     |     | Amyloid type |
|------|--------------------|-------------------------------------------------------|-------------|------------|-----|-----|--------------|
|      |                    | AA                                                    | A $\lambda$ | A $\kappa$ | AF  | TTR |              |
| 1    | ++                 | 0                                                     | (+)         | (+)        | +++ | +++ | AF           |
| 2    | +                  | 0                                                     | (+)         | 0          | ++  | ++  | AF           |
| 3    | +                  | 0                                                     | (+)         | (+)        | +++ | +++ | AF           |
| 4    | +                  | 0                                                     | 0           | ND         | +++ | ++  | AF           |
| 5    | +++                | 0                                                     | +           | (+)        | ++  | ++  | AF           |
| 6    | +++                | 0                                                     | +           | (+)        | ++  | ++  | AF           |
| 7    | +                  | 0                                                     | (+)         | 0          | +++ | ++  | AF           |
| 8    | ++                 | 0                                                     | (+)         | 0          | ++  | ND  | AF           |

\* Estimated: +, very small; ++, moderate; +++, larger deposits. \*\* AA: monoclonal (mc13); A $\lambda$  (FIS, ULI, HAR); A $\kappa$  (SIN); AF (TIE); TTR (prealbumin). Strength of immunohistochemical reaction: 0, no reaction; (+), slightly over background; +, definitely over background; ++, strong reaction, +++, very strong reaction. ND = not done.

well removed from neurological centres. When death occurred in our cases its cause was heart failure, difficult to separate in aetiology from other deaths attributed to heart failure. Fig. 2 illustrates a family (Case 1) in which the proband and her definitely affected brother probably inherited the gene from their father. Case 7 illustrates the inability to obtain a positive family history other than that of heart failure in the proband's mother. Fig. 3 (Case 5) illustrates a possible line of transmission obscured by the early death of the proband's mother. Fig. 4 (Case 6) illustrates possible transmission from the patient's father, with uncertainty entering beyond that point.

## DISCUSSION

### *Epidemiology and genealogy*

County Donegal lies in the geographical north of Ireland in the province of Ulster. It has a population of 125,112 of which 22,289 (17.8%) are in the age group 55–74 yrs (Census of Population of Ireland, 1981). Burtonpoint has a population of 330. Case 1, her brother and Case 2 were from Burtonport. Bunbeg, where Cases 3 and 7 originated, and Derrybeg, where Case 4 originated, have a combined population of 1489. All three places lie on a small part of the north-west coast of Donegal about 15 miles long (fig. 1). The clustering of 6 cases of amyloid neuropathy in such a small area with a population of about 1800 is striking. Further, an ancestor (maternal grandmother) of Case 5, who possibly had the same illness, came from Gweedore which is in the same region (fig. 1). Case 6 came from elsewhere in the same county.

The following points indicate that these cases are hereditary in nature: (1) Case 1 had a brother with the same illness, confirmed by us pathologically; (2) Cases 5 and 6 had one relation each who had a similar illness; (3) Case 2 was distantly related to case 1; (4) all cases were of the prealbumin-related immunohistochemical AF type; (5) there is a remarkable geographical distribution.

Despite the apparent confinement of the disease to a narrow area, it is probable that the condition is more widely distributed and prevalent in Northern Ireland, and may constitute a significant genetic problem. In a retrospective pathological survey (Thornton, 1983), an analysis was made of the cases of amyloidosis for the decade 1961–1970 in Belfast's largest hospital. These were classified solely into secondary and primary, the latter by inference including true primary and familial, without further categorization. There were 43 cases of 'primary' amyloidosis, in whom myeloma was diagnosed in 3 cases only. There were 31 cases of cardiac amyloidosis. The nervous system is not referred to. Thus there may exist a more major problem which requires definition. It will be also of interest to note in the future whether there appears to be epidemiological and biochemical evidence linking the condition in Northern Ireland with that in Canada and the United States, the former being a particularly popular home for emigrants.

In regard to the question of genetic background, all our patients had 'pure' Irish ancestry as far as was known and could be ascertained. HLA patterns were examined in 2 only (Cases 1, 6) and these did not differ from the general pattern in the west of Ireland population (Stevens *et al.*, 1978), nor did they conform to the suggested association with HLA 2 and HLA 9 (da Silva *et al.*, 1980).

The possibility of the mutated gene being brought into Ireland by Portuguese people was considered. There are two likely ways in which a Portuguese influence may have been introduced. First, important trade links existed between Spain and the coasts of Ireland in the 16th century (Hardy, 1966), and it is probable that there were Portuguese sailors in the ships frequenting Irish ports. Secondly, it is not generally appreciated that there was a large Portuguese element in the ships of the Spanish armada which set sail from Lisbon in 1588 (Fallon, 1978, pp. 209–210). Having been defeated by English forces, the ships took a circuitous route around the north and north-west coast and southwards by the west coast of Ireland. On this west coast 26 ships were wrecked and about 6,500 castaways landed on the shores (Fallon, 1978, pp. 211–212). Almost all were killed, there being some survivors in the northern regions. County Donegal accounted for 8 ships and 1800 castaways. Further, there is historical proof of survivors in Ballyshannon (*see fig. 1*), eight years after the defeat of the Spanish armada (Fallon, 1978, p. 53). Thus it is conceivable that mutant genetic material responsible for amyloid neuropathy was brought into Donegal by Portuguese sailors.

#### *Clinical features and natural history*

The cases in the present series are characterized by a late age of onset (range 58–68 yrs), severe generalized sensorimotor neuropathy, usually although not



necessarily with onset in the lower limbs, cardiac involvement (conduction defects, cardiomyopathy and terminal congestive failure) of a particularly devastating quality, intermittent diarrhoea and syncopal attacks. Although strongly suggestive, our data do not allow us to state definitively that the autonomic system is involved in all.

Taking clinical, pathological and immunohistochemical data together, these cases belong to the familial amyloid polyneuropathy (FAP) of Portuguese, or Type 1, form. They differ from those described by Andrade in the absence of dissociated sensory loss and in the late age of onset, which was 25–35 yrs in his cases. However, late onset can be a feature in Portuguese cases (Lima and da Silva, 1980). Late onset is the rule for the Swedish cases (Andersson, 1970). Similarly, some English cases (Zalin *et al.*, 1974), although not all (Mahood, 1980), have been of late onset. More recently, Feurle *et al.* (1984) have demonstrated late onset in one of two German kinships in whom the condition was established as being due to the deposition of the prealbumin-related AF amyloid, and Libbey *et al.* (1984) have reported similarly from the United States.

The cases described by Van Allen had an onset in the lower limbs and were of mixed Scottish-English-Irish ancestry. The Donegal cases differ from these in the lack of renal involvement and peptic ulceration, both characteristics of the cases of Van Allen *et al.* (1969). The only such feature was a benign gastric ulcer in one of our patients.

It seems clear that age of onset and other phenotypic characteristics can vary considerably for this category of type 1 familial amyloid polyneuropathy, even when a common genetic defect exists. For instance, a single amino acid substitution of methionine for valine at position 30 in the prealbumin molecule has been shown to exist in the Japanese (Tawara *et al.*, 1983), Portuguese (Saraiva *et al.*, 1984) and Swedish (Dwulet and Benson, 1983) forms. Despite the presumed homogeneity of the genetic defect for the coding of this protein, variations occur both within and between groups. Nevertheless, complete genetic homogeneity appears not to exist, and a different amino acid substitution, that of glycine for threonine at position 49 in the prealbumin molecule, has been described for a Jewish family (Pras *et al.*, 1981). Now that the abnormal prealbumin molecule can be detected in serum (Nakazato *et al.*, 1984; Benson and Dwulet, 1985), and presymptomatic diagnosis of heterozygosity is possible by recombinant DNA techniques, it becomes a matter of importance for each group to establish the exact biochemical defect in the amyloidosis with which it is dealing.

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## PROGRAMMING AND EXECUTION OF MOVEMENT IN PARKINSON'S DISEASE

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### SUMMARY

Programming and execution of arm movements in Parkinson's disease were investigated in choice and simple reaction time (RT) situations in which subjects made aimed movements at a target. A no-aiming condition was also studied. Reaction time was fractionated using surface EMG recording into premotor (central) and motor (peripheral) components. Premotor RT was found to be greater for parkinsonian patients than normal age-matched controls in the simple RT condition, but not in the choice condition. This effect did not depend on the parameters of the impending movement. Thus, paradoxically, parkinsonian patients were not inherently slower at initiating aiming movements from the starting position, but seemed unable to use advance information concerning motor task demands to speed up movement initiation. For both groups, low velocity movements took longer to initiate than high velocity ones. In the no-aiming condition parkinsonian RTs were markedly shorter than when aiming, but were still significantly longer than control RTs. Motor RT was constant across all conditions and was not different for patient and control subjects. In all conditions, parkinsonian movements were around 37% slower than control movements, and their movement times were more variable, the differences showing up early on in the movement, that is, during the initial ballistic phase. The within-subject variability of movement endpoints was also greater in patients. The motor dysfunction displayed in Parkinson's disease involves a number of components: (1) a basic central problem with simply initiating movements, even when minimal programming is required (no-aiming condition); (2) difficulty in maintaining computed forces for motor programs over time (simple RT condition); (3) a basic slowness of movement (bradykinesia) in all conditions; and (4) increased variability of movement in both time and space, presumably caused by inherent variability in force production.

### INTRODUCTION

Akinesia and bradykinesia are the most disabling symptoms of Parkinson's disease, and probably provide the clearest insights into the mechanisms of basal ganglia control of human movement (Marsden, 1982). Such clinical features are often not wholly ameliorated by the use of drugs. Many diverse methods of assessment have been used to detect and evaluate the behavioural aspects of the motor disorder (e.g., Perret *et al.*, 1970; Abramsky *et al.*, 1971). Any combination of features including delays in initiating motor responses, difficulties in adjusting to changes

in environmental demands, rigidity, tremor, as well as a loss of speed, coordination and fluidity of performance, may characterize the impairment of voluntary movement in parkinsonism.

Over the years, a number of theories have been proposed concerning the basis of the motor control impairment observed in Parkinson's disease, and these characterize the difficulty as either peripheral or central in nature. Peripheral accounts of observed motor dysfunction include a delay in proprioceptive feedback during movement (Dinnerstein *et al.*, 1962), and an overcompensating transcortical feedback system (Lee and Tatton, 1975). Central theories, by contrast, suggest that the abnormalities in parkinsonian movement are due to a central programming deficit. These include a faulty transmission of motor commands from the 'decision making' system to the effector mechanisms (Angel *et al.*, 1970), a loss of the ability to generate ramp movements (Kornhuber, 1971), and a loss of the ability to generate preprogrammed (ballistic) movements with a consequent reliance on current sensory information for motor control (Flowers, 1975, 1976, 1978*a,b*).

More recently, Marsden (1982) has proposed that the basal ganglia are responsible for the 'automatic execution of learned motor plans'. A motor plan is argued to have motor programs as the constituent elements. This hierarchical model proposes that motor plans involve the smooth integration, sequencing and execution of a series of motor programs. The difficulty parkinsonian patients have in executing sequential or simultaneous motor programs is thus seen by Marsden as reflecting dysfunction at the level of motor planning. Stein (1978) similarly suggested that the basal ganglia are involved in assembling sequences of movement. An alternative view highlights the observed abnormalities in production of individual movements, both in terms of reaction time for their initiation (Angel *et al.*, 1970; Evarts *et al.*, 1981; Bloxham *et al.*, 1984) and in terms of their execution (Draper and Johns, 1964; Flowers, 1975, 1976; Hallett and Khoshbin, 1980; Warabi *et al.*, 1986). This suggests that it is in the motor programs themselves that the difficulty arises, that is, basal ganglia disruption results in faulty programs of action (Kornhuber, 1974; Cools *et al.*, 1984). There has been much discussion in the literature concerning the nature of such motor programs in normals, for example, the time taken to assemble them in relation to the demands of accuracy, velocity and use of feedback in the movement (Keele, 1968, 1981; Schmidt, 1975; Brooks, 1979; Carter and Shapiro, 1984). While previous work with parkinsonian subjects has suggested that faulty programming of individual movements may be a major component of akinesia and bradykinesia, none has investigated both programming time and the parameters of movement (accuracy, duration, variability within individuals) together. The present study is designed to do this, that is, to investigate the ability of parkinsonian patients to program and execute movements of different programming loads where normal subjects are known to vary their RT and movement characteristics in relation to the movement required. It is thus hoped to determine the extent to which akinesia involves deficits in motor programming.

The study is therefore concerned both with the processes involved in the execution of movement and with the events which precede movement initiation.

The organization of the elements of a movement can be likened to writing a computer program. As the complexity and length of a program increases, so does the time required to write and compile it, that is, to turn it into usable machine instructions. Similarly, as the complexity of a prospective movement increases, so does the time needed to select and assemble (write) the elements of the motor program and, possibly, to turn these instructions into muscle-usable form (compile). Current thinking implies that RT varies with the complexity of the motor program, so that more complex movements require more programming time, thereby producing longer RTs. A number of studies using normal subjects have reported changes in RT contingent upon motor task demands (Klapp, 1975; Sheridan, 1981, 1984). The effect is apparent mainly in choice RT situations in which the subject cannot view the spatial and, by implication, temporal parameters of the impending movement, before entering the RT period. In this condition, time to program the movement is reflected in the RT measure.

Accepting the existence of motor programs raises the issue of preprogramming. If programming is taken to represent the selection and construction of a motor program after an imperative stimulus has been received, then preprogramming may be considered to involve any selection and preparation of the motor program *before* the imperative stimulus is received. In a simple RT (preview/precue) situation the subject can select and prepare (preprogram) the movement before entering the RT period. This reduces RT by reducing the programming required in the RT period and makes it difficult to detect a consistent relationship between RT and motor task demands. It implies that the subject can form a motor program from advance information and hold it for a short period before triggering it off when an imperative (go) signal appears later. This is clearly an important element in the learning and execution of smooth integrated movements, and a necessary basis for the development of many motor skills.

Wilson (1925) was the first to report quantitative measures showing impairment of RT in patients with Parkinson's disease. Since that time a number of studies have reported the failure to detect an impairment in RT (e.g., King, 1959), while others have supported Wilson's position (e.g., Heilman *et al.*, 1976). The diversity of results may, in part, be attributable to the patients selected for study, and to the type of task (choice or simple RT) performed. With regard to the latter factor, Evarts *et al.* (1981) found that parkinsonian patients were slower than controls in a simple RT condition, but that their performance in a choice RT condition was little different from their performance in the simple RT situation. This was an unexpected result, since Evarts *et al.* considered that parkinsonian patients would be relatively more impaired in a choice RT situation. More recently, Bloxham *et al.* (1984) have reported essentially similar data. Parkinsonian patients were slower than controls in a simple RT condition, but were not different in performance from controls on a choice RT task. They suggested that unimpaired basal ganglia

function is important for the initiation of preprogrammed movements and for the selection and maintenance of motor plans preceding voluntary movement.

In the studies of both Evarts *et al.* and Bloxham *et al.*, subjects were not required to aim at a target, but were simply required to generate movement (wrist rotation and finger lift, respectively). With no components of accuracy or extent, programming in these situations is reduced to a minimum, and as Evarts *et al.* recognized, 'further studies of RT (with tests requiring programming of displacement, velocity, and accuracy) may provide insights into the nature of the central motor disorder in Parkinson's disease'. The aim of the present study is precisely this. In this experiment three groups of parkinsonian patients and three age-matched control groups made visually-triggered arm movements, each in one of three conditions. (1) A choice RT condition in which the visually-specified target acted as the imperative stimulus for the initiation of movement. In this condition RT reflects programming time. (2) A simple RT condition in which the target appeared about 2 s before the imperative stimulus. Subjects thus had the opportunity to preprogram their movements. (3) A no-aiming condition in which subjects were simply required to generate movement in response to the imperative stimulus without having to acquire a target. This condition tested subjects' ability to initiate movements which required only a minimum of programming, but involved a RT response to an imperative signal. It also controlled for differences in the imperative signal between the choice (target as trigger signal) and simple RT (cursor as trigger signal) conditions. In order to explore the relationship between programming and execution of movement, and between akinesia and bradykinesia, aiming accuracy and movement time (MT) were also recorded.

A problem with the interpretation of RT data as a variable reflecting programming difficulty is that changes in RT related to task parameters may stem from peripheral factors such as the rate of tension development in the muscle (motor RT). It is therefore necessary to determine whether it is specifically premotor RT (which is assumed to reflect central processes) which varies with motor task demands. Premotor RT is defined as the time from the imperative stimulus until the first detected changes in EMG. Thus RT was fractionated in the present study into premotor RT and motor RT.

## METHODS

### *Subjects*

The three parkinsonian groups comprised 6 male subjects each. They were all from outpatient clinics at Hull Royal Infirmary and had a history of the disease lasting from 2 to 30 yrs. Patients were aged between 44 and 77 yrs, with the means for the three groups being, 64.3, 62.8 and 58.2 yrs, respectively. Each patient was rated independently by a doctor at six-monthly intervals on the Webster scale of symptom severity and clinical disability (Webster, 1968). They all fell into the mild or moderate range of severity; details of symptoms and treatment regime at the time of testing are shown in Table 1. Patients were tested on a 'good' day and time to minimize any possible effects of dyskinesia, tremor or fluctuation in clinical state.

TABLE 1. CLINICAL ASSESSMENT OF DISABILITY IN THE PARKINSONIAN GROUPS

|                | Subject | Age<br>(yrs) | Webster<br>score | Duration of<br>illness (yrs) | Tremor<br>(0-3) | Rigidity<br>(0-3) | Bradykinesia<br>(0-3) | Social<br>disability<br>(0-3) | Drugs                    |
|----------------|---------|--------------|------------------|------------------------------|-----------------|-------------------|-----------------------|-------------------------------|--------------------------|
| Choice RT      | 1       | 51           | 9                | 5                            | 2               | 2                 | 2                     | 1                             | Orphenadrine             |
|                | 2       | 71           | 12               | 11                           | 2               | 1                 | 1                     | 1                             | Sinemet,<br>benzhexol    |
|                | 3       | 63           | 11               | 17                           | 2               | 1                 | 1                     | 1                             | Madopar,<br>benzhexol    |
|                | 4       | 64           | 12               | 8                            | 1               | 1                 | 1                     | 0                             | Benzhexol,<br>Sinemet    |
|                | 5       | 66           | 6                | 30                           | 2               | 1                 | 1                     | 0                             | None                     |
|                | 6       | 71           | 13               | 9                            | 1               | 2                 | 1                     | 2                             | Amantadine,<br>Madopar   |
| Simple RT      | 7       | 66           | 5                | 2                            | 1               | 1                 | 1                     | 0                             | Madopar                  |
|                | 8       | 60           | 10               | 5                            | 2               | 1                 | 2                     | 1                             | Sinemet                  |
|                | 9       | 61           | 13               | 2                            | 1               | 2                 | 2                     | 1                             | Sinemet,<br>benzhexol    |
|                | 10      | 44           | 8                | 2                            | 1               | 1                 | 1                     | 0                             | Orphenadrine             |
|                | 11      | 69           | 12               | 6                            | 0               | 2                 | 1                     | 0                             | Amantadine,<br>benzhexol |
|                | 12      | 77           | 8                | 4                            | 1               | 1                 | 1                     | 0                             | Madopar,<br>orphenadrine |
| Nonaimed<br>RT | 13      | 55           | 10.5             | 2                            | 1               | 1                 | 1                     | 1                             | Orphenadrine             |
|                | 14      | 60           | 11               | 7                            | 2               | 1                 | 1                     | 0                             | Sinemet                  |
|                | 15      | 55           | 11               | 9                            | 1               | 1                 | 1                     | 1                             | Madopar                  |
|                | 16      | 74           | 9                | 4                            | 2               | 1                 | 1                     | .5                            | Benzhexol                |
|                | 17      | 56           | 4                | 3                            | 2               | 1                 | 1                     | 0                             | Orphenadrine             |
|                | 18      | 49           | 6                | 27                           | .5              | 1                 | .5                    | 0                             | Sinemet,<br>benzhexol    |

Each of the three comparison groups consisted of 6 right-handed male subjects who had no reported history of neurological problems. None of these was taking drugs which affect the CNS. The subjects were aged between 49 and 74 yrs, with the means for the three groups being, 64.8, 67 and 66.5 yrs, respectively.

Informed consent was obtained from each subject to take part in the study. All subjects were right-handed and they used this hand to perform the task.

### Apparatus

A 30 cm lever which could be moved by a seated subject was employed. A computer system was used to sample lever position and display on an 18 cm diameter cathode ray tube (CRT), positioned at eye level, 100 cm in front of the subject (*see fig. 1*). The position of the lever was represented by a spot of light (the cursor) on the CRT. The lever was free to move only in the sagittal plane, and posteroanterior movement of the lever produced a corresponding vertical movement of the cursor. Also appearing on the CRT screen was a pair of parallel horizontal lines which represented the target. The size of the target and separation from the starting position of the cursor (resting position of the lever) determined the difficulty of the task in bits, calculated according to Fitts' (1954) ratio rule (*see fig. 2*). The starting position of the cursor and of the lever which controlled its position remained constant across the different task conditions. The starting position of the cursor on the CRT screen was marked by a static 'cursor reference'. This simply consisted of a horizontal line at either side of the cursor position. Future reference in the paper will only be made to the cursor,



### *Procedure*

In order to fractionate RT into premotor and motor components, a pair of Beckman surface silver/silver chloride electrodes was placed over the anterior part of the deltoid muscle with the ground electrode sited over the external surface of the lateral epicondyle of the humerus. All electrode placements were on the subject's preferred arm. The EMG signal was amplified using a Grass Instruments preamplifier (7P3) in conjunction with a Grass driver amplifier (7DAF). EMG was recorded for 20 ms immediately before the appearance of the imperative stimulus. This recording was used by the computer to set the trigger threshold for the EMG. *Premotor RT* was the time from the imperative stimulus until the first reliably detected change in EMG. *Motor RT* was the time from this point until the first detected change in lever position. *Movement time* was the time from the start of lever movement until the completion of the movement. Premotor RT is generally considered to reflect central processes related to response programming, while changes in motor RT relate to peripheral factors such as the rate of tension development in the muscle.

After the electrodes had been satisfactorily placed on their arms, the subjects were instructed how to hold the lever and allowed to familiarize themselves with the apparatus. Instructions were to move as rapidly as possible while making as few errors as possible. As with Fitts' (1954) procedure, accuracy of performance was emphasized. Return of the lever to rest was self-paced. Subjects were not aware of the analysis of response time into premotor RT, motor RT and movement time.

The lights in the experimental room were turned off, leaving the CRT screen with the pair of target lines and cursor visible. Subjects then practised with the five different task difficulties they were going to use, until they were satisfied that they understood the task and had adapted to the illumination. In the choice RT and simple RT conditions the subjects' basic task with each movement was to wait until the imperative stimulus appeared on the CRT, and then to move the lever forward in order to move the cursor from its resting position up into the target area. In the no-aiming condition, subjects were required to move the lever forwards as quickly as possible when the imperative stimulus appeared, but not to aim specifically at the target.

### *Experimental design*

In each of the three conditions (Choice RT, Simple RT, Nonaimed RT) there were two groups of subjects, one group of 6 parkinsonians, and one of 6 age-matched control subjects. This independent-groups design was used to avoid any asymmetric transfer effect that might occur with a completely repeated-measures design (Poulton and Freeman, 1966), particularly in the parkinsonian subjects, who are known to be liable to abnormalities of mental set (e.g., perseveration) in tasks which require changes of strategy from trial to trial within a session (Lees and Smith, 1983; Flowers and Robertson 1985). In this design, therefore, each subject performed in only one condition so that the basic task remained constant throughout the session. The sequences for the conditions were as follows.

*Choice RT.* During testing, at the start of each movement, the cursor was displayed for a randomly varied period of time between 1.5–2.5 s (variable foreperiod), after which the imperative stimulus, in this case a target, was added to the display. Since subjects' cue for response was the appearance of the target, they had no preview/precue of the movement required before entering the RT period. After completing the movement, the subject placed the lever to rest and, while doing so, the position at which the movement terminated was displayed for 2.5 s, thus giving the subject knowledge of results concerning accuracy. The screen was cleared and there then followed a 2.5 s delay after which the cycle was repeated.

*Simple RT.* The sequence for the simple RT condition was similar except that, at the start of each movement, a target was displayed for between 1.5–2.5 s after which time the cursor was added to the display. The imperative stimulus in this case was the appearance of the cursor. Since the position at which the cursor appeared was the same for all movements and corresponded to the resting position of the lever, before entering the RT period subjects were aware of the response parameters of the



movement they were required to make. The rest of the cycle was the same as for the choice RT condition.

*Nonaimed RT.* The no-aiming condition was a control for any effects on RT due to the fact that the imperative stimulus was different in the choice and simple RT conditions, and as between the constant amplitude and variable amplitude movement series (*see below*). Three subjects in each group performed the choice RT condition and 3 performed the simple RT, following the same sequences as the other groups except that, instead of attempting to terminate their movements within the targets, subjects were simply instructed to respond as fast as possible to the appearance of the imperative stimulus. It was emphasized that they were not to aim at the targets, but merely to move the lever as soon as the imperative stimulus (cursor or target depending on condition) appeared on the CRT.

In line with Kerr's (1978) suggestion to avoid confusion regarding the source of possible motor task demand effects, the two movement parameters of target width and movement amplitude were varied separately. Two movement series were presented: (1) a constant amplitude (CA) series, in which the amplitude of the five targets remained the same while they varied in tolerance; and (2) a variable amplitude (VA) series, in which tolerance was held constant across the five task difficulties while amplitude varied (*see fig. 2*). The two series were constructed to produce movements with comparable task difficulties of 2, 3, 4, 5 and 6 bits. The CA series used an amplitude of 300 mm and target tolerances of 150, 75, 37.5, 18.75, and 9.375 mm. The VA series used the 9.375 mm target, but with amplitudes of 18.75, 37.5, 75, 150, and 300 mm. (The display sizes on the CRT were 40% of the movement sizes given.) Order of presentation of the series was balanced across subjects.

In each of the three conditions (choice RT, simple RT, and nonaimed RT), subjects performed the two movement series (constant amplitude and variable amplitude), each consisting of 10 practice movements followed by 50 test movements, 10 at each of the five task difficulties, presented in a random order. Any movement falling outside a set of criteria was replaced. These criteria were: MTs longer than 4000 ms; RTs shorter than 50 ms or longer than 2000 ms; and criteria related to the reliable detection of EMG. Also, if at any time the subject attempted to respond before the imperative stimulus, a warning was displayed on the CRT.

#### *Statistical treatment*

Reaction time and movement time data were analysed using analysis of variance.

## RESULTS

### *Premotor RT*

*Nonaimed RT.* With subjects simply responding as soon as the imperative stimulus appeared and not attempting to aim at the target, no differences were found between the 6 subjects (3 parkinsonian, 3 control) simulating the choice RT condition and the 6 subjects (3 parkinsonian, 3 control) performing in the simple RT condition (i.e., reaction to targets or cursor), ( $F(1,8)=1.91$ ). Similarly, no differences were found across task difficulty ( $F(4,32)=0.54$ ), nor between VA and CA series ( $F(1,8)=0.79$ ). Thus RT was not significantly affected by stimulus differences. Overall (for both Series and all Index of Difficulty (ID) levels combined), mean premotor RT was 300 ms for parkinsonian patients and 223 ms for age-matched controls (*see fig. 4*) and this difference was significant ( $F(1,8)=5.41$ ,  $P<0.05$ ). None of the other factors interacted with this effect. Movement data obtained from the no-aiming condition will be considered later.

*Choice and simple RT.* Premotor RTs for the choice RT and simple RT conditions

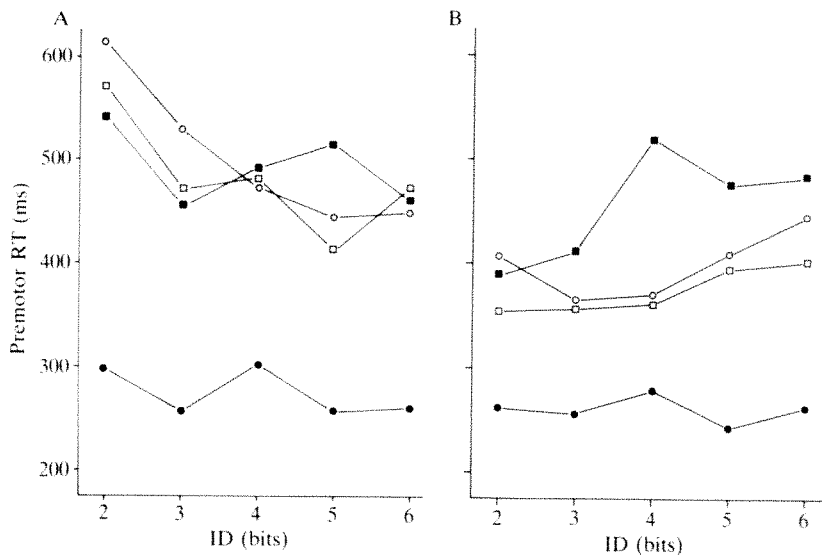


FIG. 3. Mean premotor RT in the aiming conditions, as a function of groups, by task difficulty. ID=Index of Difficulty. A, variable amplitude series; B, constant amplitude series. Squares=parkinsonian patients ( $n=6$ ); circles=age-matched controls ( $n=6$ ). Closed symbols=simple RT; open symbols=choice RT.

are shown in fig. 3 for the VA and CA series respectively, and overall (for Series and ID levels combined) in fig. 4. For the latter, the main factor of Groups, comparing parkinsonians with age-matched controls, was not significant, although the within-subject variability of the premotor RTs of parkinsonian patients was greater than for age-matched control subjects ( $F(1,20)=7.17$ ,  $P<0.025$ ). The main effect of Conditions (choice RT vs simple RT) considered for Groups, Series and ID levels combined was also not significant, but the Groups by Conditions interaction was ( $F(1,20)=4.54$ ,  $P<0.05$ ). This is the most striking effect in the RT data showing (*see* figs 3, 4) that while the parkinsonian patients and age-matched control subjects did not differ in the choice RT condition, in the simple RT situation controls were significantly quicker. The patients' performance was not, overall, significantly different between the two Conditions. Thus the patients were not abnormally slow in programming aiming movements from the starting position, but failed to reduce the time taken when given advance information about the movement required. Note that in the choice RT condition, the parkinsonian data show a similar slope to controls of RT against ID, that is, their performance shows a sensitivity to the 'programming load' of the movements, and this is true in both the VA and CA series (*see* fig. 3). This is maintained in the simple RT condition for the parkinsonian group, but not for the control group, who evidence a near zero slope by taking advantage of the advance information to preprogram movements.

All other comparisons with the Groups were not significant, and fig. 5 displays the factors of Conditions, Series (CA vs VA), and Index of Difficulty (ID) for parkinsonian and control Groups combined. In this graph, in the VA series ID

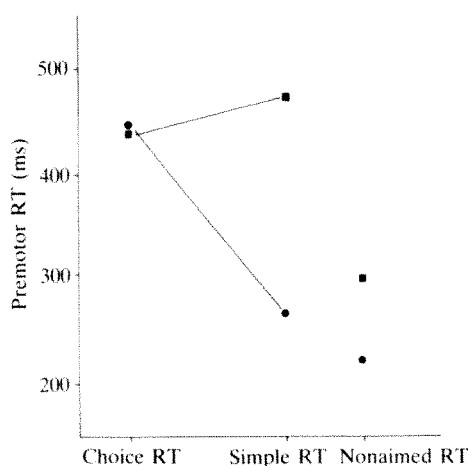


FIG. 4. Mean premotor RT as a function of groups by aiming conditions (series and ID levels combined). Squares = parkinsonians, circles = age-matched controls.

increases as the amplitude of the movement increases, while in the CA series ID increases as the width of the target decreases.

Fig. 5 shows that premotor RT in the VA series was a negative function of task difficulty, while for the CA series the function was slightly positive. In other words, for the VA series, the nearer the (small tolerance) target was to the starting position (lower ID), the longer was the premotor RT. For the CA series, small targets (higher ID) took somewhat longer to respond to. Fig. 5 reveals that the difference between the CA and VA series was greatest in the choice RT condition. Analysis indicated that the premotor RTs for the five task difficulties were significantly different ( $F(4,80)=2.80$ ,  $P<0.05$ ), as was the Conditions by ID interaction ( $F(4,80)=2.90$ ,  $P<0.05$ ). More interestingly, the main factor of Series was significant ( $F(1,20)=12.31$ ,  $P<0.01$ ), with premotor RTs in the VA series taking longer than in the CA series. Moreover, the ID by Series interaction was significant

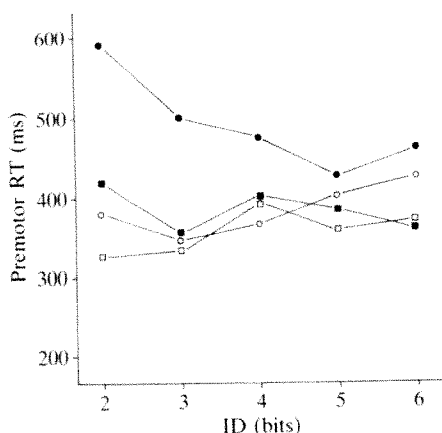


FIG. 5. Mean premotor RT as a function of aiming conditions, by series, by task difficulty (parkinsonian and control groups combined). ID = Index of Difficulty. Circles represent choice RT and squares simple RT conditions. Filled symbols represent variable amplitude and open symbols constant amplitude series.

( $F(4,80) = 8.19$ ,  $P < 0.001$ ), indicating that the lower the ID the greater the difference between premotor RTs in the CA and VA series (see fig. 5).

For age-matched control subjects the main difference between the conditions occurred for the VA series ( $F(1,10) = 12.38$ ,  $P < 0.01$ ), the form of the CA series being similar between conditions ( $F(1,10) = 2.28$ ) (see fig. 3). Within the VA series, differences between conditions for control subjects occurred to a greater extent for the lower ID levels (this apparently paradoxical result is discussed later). No differences existed for parkinsonian patients between choice and simple RT in the CA series ( $F(1,10) = 1.16$ ) or VA series ( $F(1,10) = 0.02$ ). No other comparisons were significant.

Since the order of Series presentation to subjects was balanced (CA-VA vs VA-CA), it was possible that subjects receiving the CA series first, and thus being trained on the 30 cm amplitude, may have developed a strategy of preparing for this amplitude in the VA series, thereby contributing to the effect of smaller amplitudes. To investigate this possibility a post hoc analysis of variance was performed with order of series included as a factor. Neither the main effect of Order, nor any interaction involving Order was significant.

### *Motor RT*

With regard to the motor RT data, there were no significant differences for Groups, Conditions, Series or ID. In particular, no differences were detected in motor RT between parkinsonian patients (mean motor RT 103 ms) and age-matched controls (mean motor RT 119 ms) ( $F(1,20) = 1.72$ ), although it may be relevant to note that the lever provided only minimal resistance to movement. In a similar vein, Dick *et al.* (1984) reported that the excitability and conduction velocity of the corticospinal motor pathways are normal in Parkinson's disease, and conclude that bradykinesia is due to abnormal motor commands (central dysfunction) delivered to a normal corticospinal system. The lack of effect for the other factors conforms with the finding of Goggin and Christina (1979) of only a 5 ms difference in motor RT between movement to small or large targets in normal subjects, and with the studies of Lagasse and Hayes (1973) and Anson (1982) which detected no differences in motor RT between short and long extent movements. Overall, the mean motor RT in the present study across all conditions was 111 ms.

### *Movement accuracy*

Mean error rates (overshoots and undershoots of the set target area) for the two groups were 25.83% (parkinsonian patients) and 23.67% (age-matched controls), which were not significantly different, so accuracy is comparable. Table 2 presents the pattern of error distribution across the factors of Groups, Conditions, Series and ID.

Overall, more errors were made in the simple RT (27.25%) than in the choice RT situation (22.25%) ( $\chi^2(1) = 6.06$ ,  $P < 0.05$ ). This difference was due to control subjects making fewer errors in the choice RT (17.83%) than the simple RT

TABLE 2. MEAN PERCENTAGE ERROR RATES IN AIMING CONDITIONS AS A FUNCTION OF GROUPS, BY CONDITIONS, BY SERIES, AND BY TASK DIFFICULTY

|           |                              | <i>Index of Difficulty</i> |       |      |       |       |       |       |       |       |       |
|-----------|------------------------------|----------------------------|-------|------|-------|-------|-------|-------|-------|-------|-------|
|           |                              | 2                          |       | 3    |       | 4     |       | 5     |       | 6     |       |
|           |                              | CA                         | VA    | CA   | VA    | CA    | VA    | CA    | VA    | CA    | VA    |
| Simple RT | Age-matched control subjects | 0                          | 45    | 5    | 41.67 | 15    | 41.67 | 23.33 | 41.67 | 41.67 | 40    |
|           | Parkinson's disease patients | 0                          | 45    | 6.67 | 41.67 | 13.33 | 38.33 | 16.67 | 28.33 | 31.67 | 28.33 |
| Choice RT | Age-matched control subjects | 3.33                       | 31.67 | 1.67 | 20    | 3.33  | 23.33 | 16.67 | 25    | 30    | 23.33 |
|           | Parkinson's disease patients | 0                          | 46.67 | 0    | 43.33 | 5     | 43.33 | 26.33 | 35    | 33.33 | 31.67 |

CA = constant amplitude; VA = variable amplitude.

condition (29.5%) ( $\chi^2(1)=17.25$ ,  $P<0.001$ ). There was no difference for parkinsonian patients between choice (26.67%) and simple RT (25%) conditions. Similarly, the parkinsonian patients made more errors in the choice RT condition than controls ( $\chi^2(1)=10.52$ ,  $P<0.01$ ), but there was no difference in the simple RT situation. There were, overall, more errors in the VA series (35.75%) than in the CA series (13.75%) ( $\chi^2(1)=117.33$ ,  $P<0.001$ ), and this was true for both parkinsonian patients ( $\chi^2(1)=70.66$ ,  $P<0.001$ ) and controls ( $\chi^2(1)=47.38$ ,  $P<0.001$ ). The difference between the CA and VA series was also present for the simple RT ( $\chi^2(1)=62.54$ ,  $P<0.001$ ) and the choice RT situations ( $\chi^2(1)=54.84$ ,  $P<0.001$ ).

With regard to the differences across task difficulty, there was a difference for the CA series ( $\chi^2(4)=134.3$ ,  $P<0.001$ ), but not for the VA series ( $\chi^2(4)=5.14$ ). This pattern of error difference for the CA series across ID with no difference for the VA series, was repeated both for parkinsonian patients and controls under simple and choice RT conditions. Since errors for the high ID tasks were not different between Series, the effect reflects the fact that in the CA series subjects made fewer errors on the low ID (wider target) tasks. This was not simply the result of producing the most accurate movement (i.e., as for the ID 6 task) for all of the target tolerances, since a post hoc analysis of the movement-endpoint variable error produced a significant difference between the five task difficulties ( $F(4,80)=14.21$ ,  $P<0.001$ ), and a significant interaction between Series and ID ( $F(4,80)=4.75$ ,  $P<0.01$ ). Thus variable error remained nearly constant in the VA series, but increased in the CA series for targets with greater tolerance. No other comparisons were significant. Subjects thus made fewer errors with wide tolerance targets at the same time as increasing variable error. In addition, they moved more quickly.

The percentage of movements falling outside the various criteria for RT, MT,

and the reliable detection of EMG, were 10.92% (parkinsonian patients, choice RT), 8.17% (parkinsonian patients, simple RT), 7.83% (age-matched controls, choice RT) and 4.58% (age-matched controls, simple RT). These movements were replaced within trials. The relatively small rejection rates make it unlikely that the included responses were biased by the selection criteria, for example, to include only abnormally good responses in the parkinsonian group. This conclusion is reinforced by the fact that the rejection criterion for RT was over 4.4 times higher, and the rejection criterion for MT was over 3.4 times higher, than actual mean parkinsonian performance. These data argue against the operation of any ceiling effect.

### *Movement time*

Parkinsonian patients moved on average nearly 37% more slowly than the age-matched control subjects ( $F(1,20)=6.84$ ,  $P<0.025$ ) (see fig. 6). Moreover, the within-subject variability of the MTs of parkinsonian patients was greater than that of the age-matched control subjects ( $F(1,20)=5.44$ ,  $P<0.05$ ), the mean SDs being 342 ms and 201 ms for patients and controls, respectively. These effects are illustrated in the individual records of fig. 7, which show examples of performance in the CA Series (ID 3) and VA Series (ID 6). Even when attempting a 'ballistic' type movement (as in fig. 7B) the parkinsonian subject is slower, and in this mode shows a greatly increased endpoint variability. It should be noted that the records shown in fig. 7 (A, B, E, and F), although illustrating typical abnormalities of parkinsonian movement, do not represent the more extreme examples of degraded performance (see fig. 7I).

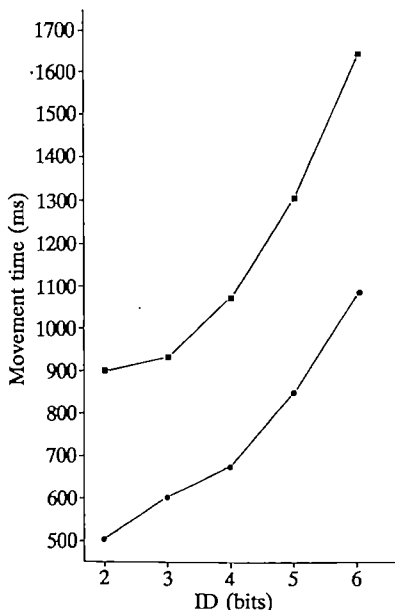


FIG. 6. Mean movement time as a function of groups, by task difficulty (series and aiming conditions combined). The squares represent parkinsonian patients ( $N=12$ ) and the circles age-matched controls. ID = Index of Difficulty.

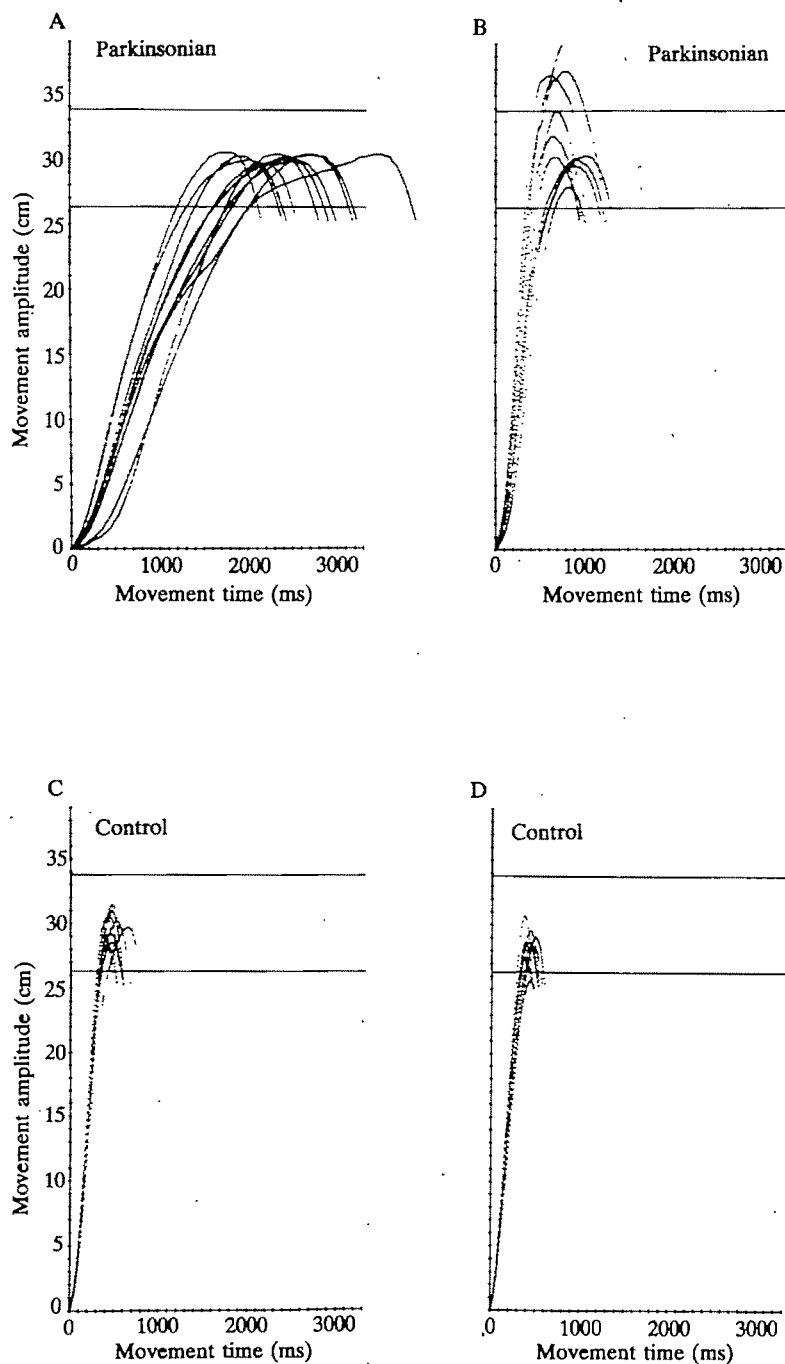
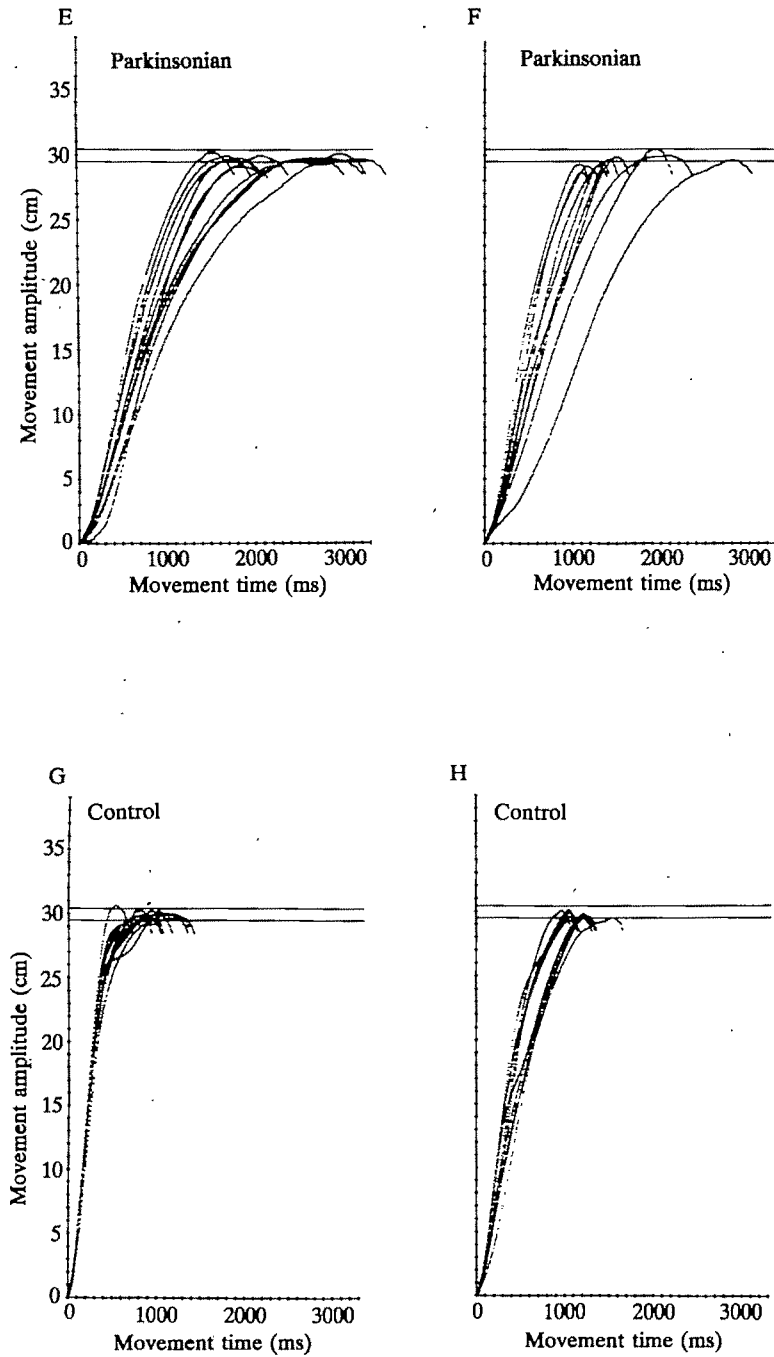
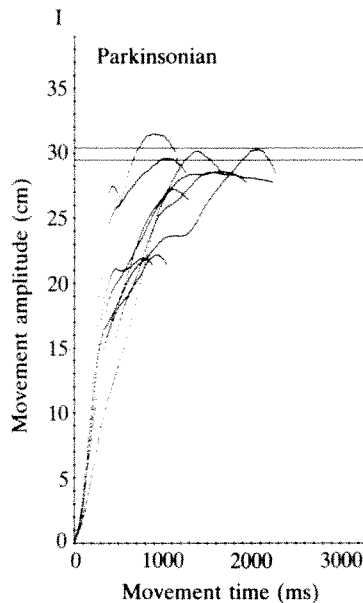


FIG. 7. (Continued on next page). Movement traces of parkinsonian and control subjects (simple RT condition): A-D are from the constant amplitude series (ID3), and E-I are from the variable amplitude series (ID6). Each record A-I represents the performance of a different subject and displays the 10 movement traces made by the subject in that particular series and ID level. Each successive point on a movement trace represents 5 ms in time (i.e., 200 Hz sampling rate), with analogue-to-digital conversion of distance being to 12 bit accuracy.

FIG. 7. *Contd.*



FIG. 7. *Contd.*

The Groups by ID interaction was significant ( $F(4,80) = 2.78$ ,  $P < 0.05$ ), as represented in fig. 6. For the task difficulties of 3, 4, 5 and 6 bits, there is an increasing MT difference between parkinsonians and controls. The MT difference for the task difficulty of 2 bits is also greater than for the 3 bit task. Even the 2 bit task took longer than 300 ms to complete and this allows the possibility of visual control in the movements under discussion. As expected, the main factor of ID was significant ( $F(4,80) = 110.85$ ,  $P < 0.001$ ), as was the Series by ID interaction ( $F(4,80) = 17.25$ ,  $P < 0.01$ ). No other comparisons of total movement times were significant. The only other point of note related to the MT data was that the within-subject variability was significantly greater in the choice RT condition than in the simple RT condition ( $F(1,20) = 6.40$ ,  $P < 0.025$ ).

The MT data were further broken down into the first half and second half of the movement distance. The first half was taken as being more likely to reflect the ballistic phase of the movement, or in Woodworth's (1899) terms the 'initial impulse', while the second half of the movement involves more of the process of 'current control'. While obviously this operational division of movement does not separate it precisely into the two phases, the movement times of the two halves will reflect proportionally the ballistic and control components. Separate analyses of variance were performed on the MTs of the first and second halves of the movement. For the first phase of movement the main factor of Groups was significant with patients taking longer than controls ( $F(1,20) = 7.87$ ,  $P < 0.025$ ). Also the within-subject MT variability was greater for patients ( $F(1,20) = 7.30$ ,  $P < 0.025$ ). These effects show that the abnormalities of parkinsonian movement production, such as increased spatiotemporal variability, appear even in the early stages of the move-

ment and, as can be seen in the individual records of fig. 7, often within a few hundred milliseconds of the start.

The Groups by ID interaction was significant ( $F(4,80)=5.16$ ,  $P<0.01$ ), as was the Groups by Series by ID interaction ( $F(4,80)=4.61$ ,  $P<0.01$ ). The latter interaction reflects the fact that the difference between the MTs of patients and controls was relatively constant across ID for the CA series, while for the VA series parkinsonian patients were increasingly slower than controls with increasing ID. As expected, the main factor of ID was significant ( $F(4,80)=89.81$ ,  $P<0.001$ ), and the Series by ID interaction was significant ( $F(4,80)=46.60$ ,  $P<0.001$ ). No other comparisons of the first phase MT were significant.

For the second phase of movement, the main factor of Groups was significant ( $F(1,20)=5.70$ ,  $P<0.05$ ), with patients taking longer than controls. Again this is illustrated in the individual records of fig. 7. The main factor of Conditions was significant ( $F(1,20)=4.67$ ,  $P<0.05$ ) with second phase MT in the choice RT condition being greater than in the simple RT condition for both groups. Within-subject MT variability was also greater in the choice than simple RT situation ( $F(1,20)=7.19$ ,  $P<0.025$ ). Again as expected, the factor of ID was significant ( $F(4,80)=77.28$ ,  $P<0.001$ ), as was the Series by ID interaction ( $F(4,80)=8.96$ ,  $P<0.001$ ). No other comparisons of the second phase MT were significant.

In the no-aiming condition, subjects were simply asked to generate a forward movement of the lever in rapid response to the imperative stimulus, and were instructed not to aim specifically at the target. There was no difference in MT between parkinsonian patients and age-matched controls ( $F(1,8)=0.48$ ); however, controls moved further than patients in this unconstrained situation, and thus moved significantly faster ( $F(1,8)=17.13$ ,  $P<0.01$ ). Average movement velocities were  $77\text{ cm}\cdot\text{s}^{-1}$  for patients and  $112\text{ cm}\cdot\text{s}^{-1}$  for controls. Interestingly, when the within-subject movement endpoint variability was analysed, the parkinsonian patients were found to be significantly more variable than controls ( $F(1,8)=5.68$ ,  $P<0.05$ ). Variability is measured in terms of the SD of the movement endpoints about their own mean (see Schmidt *et al.*, 1978); this is referred to as effective target width ( $W_e$ ). For patients this was 3.79 cm and for controls 1.76 cm.

## DISCUSSION

The RT data from the present study substantiate systematically the findings of Flowers (1978*b*), Evarts *et al.* (1981) and Bloxham *et al.* (1984) in showing that parkinsonian patients seem unable to make use of advance task information to reduce their RT. Fig. 4 shows that premotor RT was found to be greater for parkinsonian patients than normal age-matched controls in the simple RT condition, but groups did not differ in the choice RT condition. Premotor RT is generally considered to reflect central factors related to response programming and was therefore selected as the measure of movement initiation time in the present study. The most plausible interpretation of this finding is that, unlike normal

subjects, parkinsonian patients are unable to use the advance information available in simple RT (preview/precue) situations to speed the initiation of the response. In a simple RT situation, normal subjects can preprogram (select and prepare) the movement before entering the RT period. This reduces RT by reducing the programming required in the RT period. Patients with Parkinson's disease seem unable to operate successfully in this fashion.

There are a number of hypotheses which could potentially account for this finding. Parkinsonism may preclude patients from programming a response before they receive an external trigger to respond (the imperative stimulus), with the advantage of advance information therefore being lost. It is known that patients have difficulty triggering the initiation of movement (Martin, 1967), particularly where the trigger for movement is internal (Wing and Miller, 1984). In the present study an external trigger was used, but in any event a basic problem with initiating the response need not preclude preprogramming of the movement. Indeed, Bloxham *et al.* (1984) argued that patients can hold some information about a movement in store between one response and the next. The capacity to store information may, however, be impaired by basal ganglia dysfunction. Buchwald *et al.* (1975) suggested that the basal ganglia are involved in the transfer of information 'across a period of time before a response is initiated'.

If one accepts the view that the motor program can be stored in short-term motor memory (STMM) until the response is initiated (Klapp, 1976), then it may be that with basal ganglia dysfunction the program degrades more quickly, caused potentially by both increased system noise and interference due to programming other responses. Thus although the motor program may not be lost in its entirety, aspects of it may need to be recomputed. This would account not only for the longer simple RTs observed in the parkinsonian group, but also for the increased within-subject variability found in the present study. Thus in a simple RT situation, patients are slower to initiate movements, and more variable in initiation time than age-matched controls. The concept of increased variability of performance for the parkinsonian patients will be a recurring theme.

In the no-aiming condition, subjects have simply to generate movement, and with no components of accuracy or extent to be specified, programming is reduced to a minimum. Fig. 4 displays the attendant reduction in RT observed for both groups. It appears evident that where final spatial location of movement is a relevant factor, more time is required to program the movement. While this is true for both patients and controls, the difference between conditions is much greater for the patients. More detailed inspection of the patients' data revealed that the smallest difference between simple and nonaimed RT conditions occurred for movements with greatest target tolerance (2 and 3 bit tasks in the CA series). With large target tolerance there is less need to compute exactly the endpoint of the movement. In such a situation patients need to do less reprogramming of the degraded program, and movement can be initiated more quickly. The difference between patients and normals for RT in the no-aiming condition suggests that

patients have a basic problem in initiating movement, as others have reported (Bloxxham *et al.*, 1984), in addition to their difficulty in holding a motor program in memory.

Evarts *et al.* (1981) speculated that task parameters such as accuracy and extent might affect RT differentially for parkinsonian and control subjects. Although patients took longer than controls to initiate movements in the simple RT condition, there were no systematic differences in RT between groups dependent on the parameters (accuracy or extent) of the impending movement. This fact, coupled with the lack of difference between groups for choice RT, suggests that the ability of patients to construct motor programs is little impaired. This statement does not imply that the *output* from the constructed program is as accurate in spatiotemporal definition as for normals. Inferior motor performance may be caused either by faulty sensory to motor transformation (i.e., an inappropriate program is constructed), or by defective motor output from a noisy system. In any event, particular problems arise when the task is such that the program has to be held in store for a period of time. Here, patients display a sensitivity to 'programming load' which controls do not.

The RT data for groups combined are displayed in fig. 5, and are very similar in form to data reported by Sheridan (1981, 1984). The differences between conditions for the VA series, however, derive predominantly from the performance of the age-matched controls, as fig. 3 reveals. For patients, the data do not differ for series and task difficulty between choice and simple RT conditions. The performance of the patients is not altered by the presence of advance task information. RTs in the present study are longer than in the earlier studies. This is due to the use of older subjects and parkinsonian patients, compared with younger subjects without motor impairment in the earlier studies.

As Kerr (1978) suggested, the class of movements is important and differences exist between the CA and VA series. Considering the VA series, it is argued that for the age-matched controls any difference between the choice and simple premotor RT data is a reflection of the time required to select and prepare (program) the response, with short amplitude (small target tolerance) movements seeming to require more programming time. The data for patients also displays the latter trend (*see* fig. 3). It has been suggested that such low velocity movements present additional programming difficulties which lengthen RT (Falkenberg and Newell, 1980; Sheridan, 1984). For the CA series, the relationship across task difficulty is rather less different for the choice and simple RT conditions. This is perhaps not surprising, since a similar initial phase of the movement could be used for the different target tolerances (Langolf *et al.*, 1976). In other words, the subject could start to move on perceiving the imperative stimulus, and only later adjust the movement with visual control if necessary. Clearly, this strategy would not work in the VA series, since it would result in overshooting the nearer targets.

As detailed in fig. 6, even the tasks performed most quickly had MTs greater than 300 ms. Thus movements in the present study took sufficient time to involve

visual control—and yet premotor RT was still affected. As the first phase of even controlled movements is presumably programmed in advance, then there is no reason to limit programming effects on RT to short ballistic movements, as has been attempted (Klapp, 1975). Indeed, in some models it is argued that where greater accuracy is required the average velocity of the entire movement is reduced to bring the final visual correction nearer to the target (Howarth *et al.*, 1971, Beggs and Howarth, 1972). This view suggests that any such alteration to the program would necessarily have to be computed before the movement commenced, thus affecting RT.

The present data do not seem to derive from particular response strategy options adopted by subjects, and thus reflect programming changes. This has been considered in detail elsewhere (Sheridan, 1984). Moreover, the results cannot be explained by a confounding of stimulus and response factors related to eccentric angle (angle between the centre of the field of vision and the target), and visual angle (dependent upon the size of the target within the visual field). Christina and Cornell (1979) have argued that the further into the periphery targets occur, the greater the latency of eye movement to the target, and the more difficult the target is to detect, hence lengthening RT. Since the maximum eccentric angle in the present study was less than 5 deg, these problems seem not to apply. Furthermore, results from the no-aiming condition indicate that the reported premotor RTs were not due simply to stimulus detection factors, but reflect response programming. The influence of the stimulus encoding process may not be entirely ruled out in the choice RT data. It is, however, not necessarily useful to distinguish stimulus encoding from response programming, since visual analysis of the task parameters may be very intricately linked to the formation and maintenance of the response program. Encoding the task parameters may operate in parallel with the process of constructing the response program.

Overall, the movement accuracy of the patients and age-matched controls did not differ, thus the MTs presented in fig. 6 are directly comparable. The only difference between groups was that controls made fewer errors in the choice RT condition. In terms of speed-accuracy trade-off this suggests that the observed difference in MT between groups for the choice RT condition is probably an underestimate. Groups differed in speed of movement with patients displaying bradykinesia. This effect was present in both the first and second phase of movement. The parkinsonian group moved, on average, nearly 37% more slowly than the age-matched controls (*see* fig. 6). Within-subject MT variability was also greater for patients (fig. 7). As figure 6 shows, there is an interaction between groups and task difficulty. For tasks 3 to 6 bits there is an increasing difference in MT between groups. In formulating his task taxonomy, Fitts (1954) argued that the higher the index of difficulty, the greater the precision required in the movement. The achievement of high precision usually implies the increased involvement of visual guidance (e.g., Crossman and Goodeve, 1963). Thus the greater the precision required, the slower patients' movements need to be to allow increased visual

guidance. Indeed, for both movement series, the difference between the first and second phases of movement is greater for patients than controls, allowing increased opportunity for visual guidance. This slowing of movement is proportionally greater in patients than controls because of the higher inherent variability of patients' movements. Put simply, they are uncertain how far their hand is going to move. Statements made by patients support this view, for example, 'I know what I want to do, but my hands won't do it'. Patients' problems with employing normal predictive strategies during visual tracking tasks (Flowers, 1976, 1978*a,b*) are not caused by an inability to form an 'internal model' of the track, but by their difficulty in forming 'a dynamic "internal model" of their own movements' (Flowers, 1978*a*). Patients are uncertain exactly where their movements will go. Thus, although they can adopt predictive strategies, they cannot make normal use of predictive action to reduce tracking error to the same extent as controls (Flowers, 1978*a,b*, Day *et al.*, 1984). For simple predictive tracks not involving the initiation or selection of different movements, the performance of patients can be relatively good (Bloxham *et al.*, 1984).

Where there is a specific accuracy requirement, as in the present aiming conditions, the greater movement variability is expressed in terms of lengthened MT and greater within-subject variability in MT. However, where accuracy is unspecified, as in the present no-aiming condition, variability is expressed in the increased dispersion of a patient's movement endpoints. Greater force of movement results in greater variability of movement endpoints (Schmidt *et al.*, 1978). Within-subject variability of movement endpoints ( $W_e$ ) was greater for patients, and yet they moved more slowly than controls, reinforcing the significance of the variability effect. Variability ( $W_e$ ) as a percentage of distance moved was 14.9% for patients and 4.5% for controls.

In normal subjects, EMG shows a characteristic triphasic pattern of agonist and antagonist activity associated with rapid voluntary movement. Hallett and Khoshbin (1980) have shown that parkinsonian patients cannot, however, generate sufficient EMG activity in the initial agonist burst to achieve the required force for a large fast movement. To compensate for the overall downward scaling of activation of the triphasic pattern, patients attempt rapid movements by repeated cycles of alternating agonist and antagonist activity. Although activation (energizing) of the muscle is impaired, timing and muscle selection remain intact. The latter components are argued to be under direction of the cerebellum. Recent work suggests that it is an over-simplification to argue that in Parkinson's disease there is a strictly limited amount of 'energy' available for fast movement. Berardelli *et al.* (1986) report that the amount of EMG activity in a wrist flexion movement does not saturate, but can be modulated, within limits, to the size of the movement required. Parkinsonian movement was slower overall and the agonist burst was seen as being inappropriately scaled to the movement amplitude and velocity. The present study suggests that there is also increased variability of movement. Further work may reveal more directly if this is due to inherent variability in force production.

A tentative synthesis of the data can be attempted. Marsden (1984) concludes that 'the overall form of motor programmes is preserved in Parkinson's disease, in that the selection of muscles and the relative timing of their activation is intact. However, the details of the number and frequency of motor neurons activated, at least in the first agonist burst, are inaccurate'. Similarly, one could argue that the schema (Schmidt, 1975), or basic algorithm, for a particular movement remains intact, but that the generation of force is impaired. The failure to generate force correctly may be more than a basic failure to energize the muscles sufficiently, as Berardelli *et al.* (1986) argued. The increased variability of parkinsonian movement observed may derive from any or all of the following defects: (1) incorrect computation of the required forces; (2) defective memory for computed forces; and (3) noisy output from the motor system. Such potential defects in the forcing function of the motor program may compound across time, leading to such things as micrographia, and the pattern of RTs observed.

The motor dysfunction displayed in Parkinson's disease can be seen to involve a number of components. (1) A basic problem with simply initiating movement, which can extend to akinesia. (2) Difficulty in maintaining the computed forces for the program over time. (3) A basic slowness of movement (bradykinesia). (4) Increased variability of movement, presumably caused by inherent variability in force production. While the evidence is, as yet, insufficient to do more than speculate, much of the data could be explained by a model of abnormal basal ganglia function involving the rapid decay or disruption of computed force. Over and above such defects in programming and executing simple movements there may be problems related to the smooth integration, sequencing and execution of a *series* of motor programs (Marsden, 1982, 1984). Such motor planning is outside the scope of the present discussion.

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# CATEGORIES OF KNOWLEDGE

## FURTHER FRACTIONATIONS AND AN ATTEMPTED INTEGRATION

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### SUMMARY

In this study we investigated the category specificity of the comprehension impairments of Y.O.T., a patient with a severe global dysphasia. Using matching to sample techniques it was possible to demonstrate selective impairments and selective preservations not only of broad categories of semantic knowledge but also of particular subsets of such categories. Specifically, Y.O.T.'s comprehension of 'objects' was, in general, significantly more impaired than for foods or living things. Within the broad class of objects she was significantly more impaired in the comprehension of small manipulable objects than large man-made objects. Within her proper noun vocabulary there was a significant dissociation between her good comprehension of proper nouns having a unique and well-known referent (e.g., Churchill) and common proper nouns without such a referent (e.g., Jones). Her error responses were not consistent, semantic similarity and significant rate effects were observed, and it was therefore considered that her category specific comprehension deficits were primarily ones of access to a full semantic representation.

We attempt to give a principled account of the increasing number of seemingly arbitrary instances of fine-grain categorical impairments of semantic knowledge. We have suggested that different weighting values from multiple sensory channels will be important in the acquisition of different categories of knowledge and that such differential weightings could be the basis of the categorical organization of systems in the brain subserving semantic knowledge.

### INTRODUCTION

Since the midnineteenth century there have been sporadic reports of comprehension deficits in aphasic patients that are consistent with the view that knowledge systems are categorical in their organization. More recently these early anecdotal accounts have been substantiated in a series of investigations using quantitative methods, and highly selective dissociations between different classes of knowledge have now been documented.

The possibility that such classical clinical neurological dissociations could be interpreted in terms of a category specific model of semantic processing was first discussed in the context of impairment of *concrete* word knowledge as compared

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with the preservation of *abstract* word knowledge. This dissociation was documented in a patient whose other language and intellectual skills were well preserved (Warrington, 1975). This selective impairment of the concrete word vocabulary has now been confirmed in a second case (Warrington and Shallice, 1984). It is apparent, however, that fractionations may occur within the broad category of concrete words both in word retrieval and word comprehension.

In a study of naming and comprehension in aphasic patients, Goodglass *et al.* (1966) reported a double dissociation between two classes of concrete or imageable words, that is, the naming and comprehension of action names and object names (*see also* Miceli *et al.*, 1984). More recently we have described a patient whose naming and comprehension vocabulary for action verbs was gravely depleted. At the same time his knowledge of common nouns and proper nouns was well preserved. In particular, his ability to name famous people and geographical places was excellent (McCarthy and Warrington, 1985). There is evidence that the class of proper nouns itself fractionates; the selective preservation of the retrieval of place names together with the selective impairment of the names of famous personalities is on record (McKenna and Warrington, 1980).

Typically, and for good practical reasons, language skills of aphasic patients are frequently assessed clinically by asking them to name or point to small manipulable objects or parts of the body. Perhaps this accounts for the early discovery of the classical syndrome autotopagnosia! These categories may be quite inadequate to describe an individual's concrete word vocabulary and indeed the observations of Nielson (1958) bear this out. He reviewed the clinical literature and claimed that there was a selective loss of knowledge of living things in 6 cases and that the knowledge of man-made objects was selectively impaired in 9 cases. These observations were interpreted in terms of a distinction between knowledge of animate and inanimate categories.

In a quantitative study of 4 patients (all recovering from Herpes simplex encephalitis), selective preservation of the comprehension of specific object knowledge was recorded (Warrington and Shallice, 1984). The language skills of 2 of these patients (JBR and SBY) was sufficiently intact for word definition tasks to be employed. In contrast to their adequate object knowledge they were severely impaired in their ability to define animal, plant and food names. There was a similar pattern of performance in their identification of pictures. The other 2 patients (KB and ING) whose expressive language skills were severely impaired, were tested using spoken word to picture-array matching tasks; for both of these patients there was a disproportionately high error rate with the food and the animal arrays as compared with arrays of common objects.

Any suggestion that these dissociations could be accounted for in terms of, for example, word frequency, age of acquisition, or familiarity can be discounted almost entirely on the basis of our earlier documentation of the opposite pattern of impairment in a single case, VER (Warrington and McCarthy, 1983). Using verbal/visual matching tasks it was shown that the category 'objects' was dis-

proportionately impaired in comparison with the other 3 categories which were sampled (food, animals and flowers). These data therefore provide evidence of a double dissociation between knowledge of objects on the one hand and living things and food on the other.

We have previously argued for a refinement of the animate/inanimate dichotomy and suggested that a distinction cast in terms of the relevant salience of processing functional/physical (also termed sensory) attributes might account for these dissociations. Thus similar items from the broad category of objects are primarily comprehended in terms of their core functional significance, physical attributes being of less importance for their differentiation (e.g., shoes and slippers, handbag and briefcase, gate and stile). Foods and living things by contrast are differentiated primarily in terms of their physical attributes (e.g., carrot and parsnip, canary and robin, snowdrop and crocus). This formulation is somewhat strengthened by a more detailed analysis of J.B.R.'s responses to a wide range of categories. Thus it should be noted that one animate category with strong functional significance, namely body parts, was among his preserved categories, two inanimate categories whose exemplars are differentiated mainly by their physical attributes were among the impaired categories (precious stones and fabrics). While this dichotomy has a certain plausibility, it is almost certainly an over-simplification. It would appear that this typology is at the same time too broad and too narrow. First, there is some evidence that points towards the possibility of fractionation *within* the categories objects and foods themselves. For example, Yamadori and Albert (1973) described a patient who appeared to have more difficulty with comprehending the names of 'indoor' objects, the knowledge of large outdoor object names being preserved. Hart *et al.* (1985) described a patient with a highly specific nominal dysphasia for common fruits and vegetables (comprehension of these names was stated to be intact). Secondly, it is obvious that the physical/functional dichotomy does not come close to encompassing the entire range of concrete or imageable concepts. What about action verbs, names of people, places, and so on?

We have recently had the opportunity to investigate a patient who showed an identical pattern of category specificity as our previous case, V.E.R. (Warrington and McCarthy, 1983), namely the preservation of animals, foods and flower names. Our aim was to explore the limits of Y.O.T.'s residual comprehension skills using a wide range of stimuli. This enabled us both to investigate the possibility of further fractionations within the broad category of 'objects' and also to explore some categories not encompassed by the physical/functional dichotomy. First we report evidence for a selective impairment in the comprehension of common manipulable objects compared with large 'outdoor' objects and secondly, the remarkable preservation of certain categories of proper noun knowledge.

#### CASE REPORT

Y.O.T., a 50-year-old previously healthy right-handed English woman, was admitted to the Centre Hospitalier D'Annecy, France, on 28.8.84, following the sudden onset of right-sided weakness and

aphasia, at which time an episode of supraventricular tachycardia was recorded. A left carotid angiogram demonstrated occlusion of the left middle cerebral artery. Eleven days later, on 8.9.84, she was transferred to the National Hospital. On neurological examination there was a dense right hemiplegia; there was no movement in either the arm or leg and facial movements were also impaired. Sensation was considered to be impaired in the right limbs and she did not respond to stimuli in the right visual field. She was globally aphasic in so far as she was unable to speak and her verbal comprehension was severely impaired.

A CT scan showed an ill-defined area of low density in the left temporoparietal region and the left lateral ventricle was larger than the right (*see fig. 1*). Serial electrocardiograms showed symmetric T

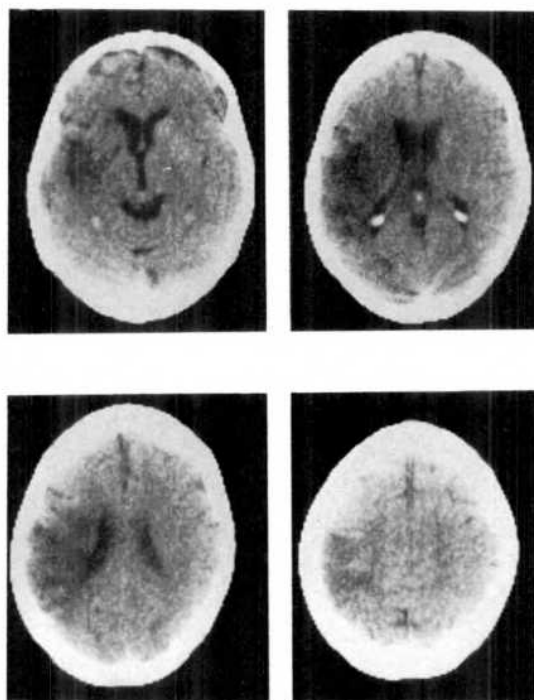


FIG. 1. CT scan of Y.O.T. showing an extensive left hemisphere infarction.

wave inversion in the lateral chest leads which gradually resolved. The infarction was considered probably to have been the result of thromboembolism.

Y.O.T. was referred to the Psychology Department on the 27.9.84 for a more detailed assessment of her dysphasia and other cognitive skills. She was tested on most days until her discharge on 15.10.84. Although Y.O.T. was alert and cooperative she was totally unable to produce any propositional speech. Her verbal utterances were restricted to the words 'yes', 'no' and 'alright', not necessarily used appropriately. Her ability to comprehend spoken language appeared to be equally gravely impaired. Her ability to nod or shake her head appropriately in response to simple questions was unreliable. She was totally unable to name common objects, or read written words aloud. She was unable to repeat any simple sounds, words, digits or to complete common phrases.

She was unable to attempt any of the verbal tests of the WAIS. Her performance IQ was only 75 (prorated from 3 test scores: Picture Completion 6, Block Design 6, and Picture Arrangement 3

(age-scaled), respectively) which we interpret as reflecting a degree of constructional and visual interpretative difficulties. However, on the Advanced Progressive Matrices Set A she scored comfortably within the average range (7/12) (Warrington, 1984). On the 28.9.84 she failed to reach a 'basal' level on the Peabody (Form B) scoring only 6 correct on the first 10 items and 31 correct on the first 50 items. Three days later she was retested on Form A on which she scored 43/50 on the first 50 items. Her ability to point to one of 4 primary colours (red, green, blue and yellow) was unreliable. She scored 21/32 correct with a response-stimulus interval of 15 s and her score dropped to a chance level (11/32) with a shorter response-stimulus interval of 2 s.

Her ability to comprehend the written word also appeared to be gravely impaired. On a modified version of the Peabody Picture Vocabulary Test (Form B) in which she was required to match the printed word to a picture, she scored 38 correct on the first 50 items. She scored 13/18 in pointing to 1 of 6 letters in an array (each presented 3 times). In an identical task using numbers she scored 18/18 correct. Her ability to match a spoken word to a written word was also impaired. For example, she was only able to score 3/18 correct in pointing to 1 of 6 common adjectives (each presented 3 times) and 2/18 correct in pointing to 1 of 6 common verbs. She scored at a similar chance level (6/20) on a similar task requiring her to point to 1 of 4 1-syllable nonsense words (each presented 5 times). Thus there is no evidence of any sparing of the phonological reading process.

In an attempt to assess the status of her visual semantics an extended version of the McCarthy and Warrington (1986) visual/visual matching test, in which the subject is required to match 2 visually dissimilar pictures of the same type of object (e.g., 2 cars, 2 brushes, etc.) was administered (*see* fig. 2). On the original 30 items (each presented 4 times in a 5-item array) her score was 83/120 which is very comparable to the performance of a patient (FRA) with a selective visual associative agnosia (McCarthy and Warrington, 1986). However, on one additional set, namely of animals (e.g., two very different line drawings of a horse and a cow, etc.) her visual/visual matching score was 20/20. We would argue from these results, together with her relatively poor scores on the Picture Completion and Picture Arrangement subtests of the WAIS that her comprehension of visual stimuli (with the possible exception of animals) was not spared, albeit that her verbal comprehension appeared to be much more impaired.

Her relatively good performance on the animals version of the visual/visual matching test alerted us to the possibility that her comprehension difficulties might be category specific. In the following series of experiments our aim is to document Y.O.T.'s residual comprehension capacities and to explore her knowledge using an extensive vocabulary from a wide range of verbal categories.

## EXPERIMENTAL INVESTIGATIONS

### *General procedures*

In this series of experiments, Y.O.T.'s residual verbal comprehension capacities were investigated using matching to sample techniques. She was asked to match each stimulus by pointing to one item of an array displayed on a desk. Each experiment was preceded by a few practice trials. The test instructions were communicated by gestures and she generally appeared to understand what was required of her quite quickly. She was tested with arrays of either 5 or 6 items in blocks of 20 or 18 trials, respectively. Thus each item was probed either 4 times or 3 times and they were presented in a pseudorandom order in each block. Although she was under no pressure to respond rapidly and self-corrections were accepted, the response-stimulus interval (RSI) was a fixed 2 s unless otherwise stated (that is a fixed interval was interpolated between Y.O.T.'s response and the presentation of next stimulus in any block of trials). She was not given knowledge of results. In

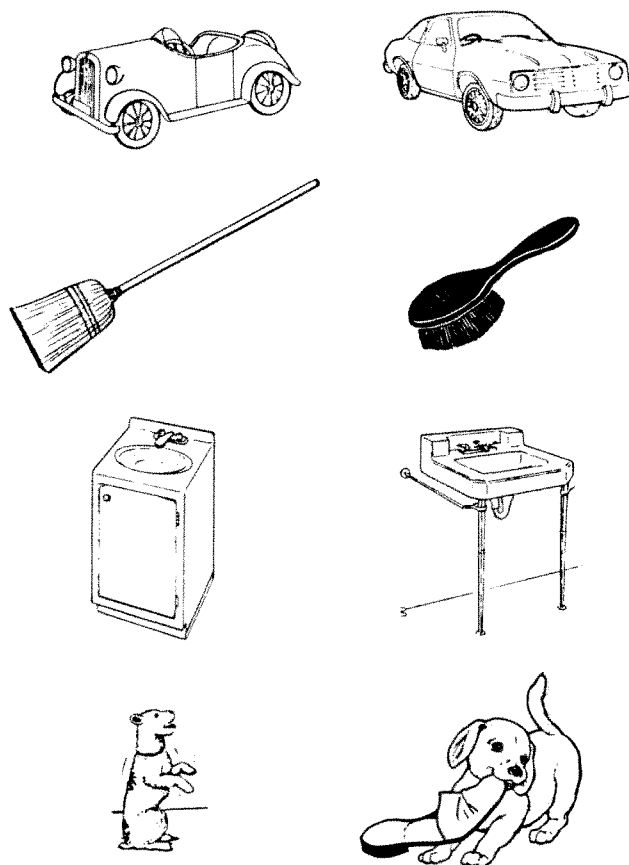


FIG. 2. Four examples of visually dissimilar stimuli from visual/visual matching test.

the first 2 experiments we report a replication of our previous observations in a patient (V.E.R.) with a category specific dysphasia in whom the verbal knowledge of common objects appeared to be selectively impaired (Warrington and McCarthy, 1983). Five further experiments describe our exploration and documentation of a wider range of categories using both pictorial and written stimulus arrays.

*Experiment 1. Category specificity: flowers, animals, objects*

In our previous case of semantic access dysphasia it had been observed that the category 'objects' was impaired as compared with flowers and animals in a two-choice word-picture matching test. Our aim in this experiment was to establish whether this same dissociation could be replicated with a larger pool of stimulus items.

*Procedure.* The test stimuli consisted of three arrays of 5 flower pictures, of 5 animal pictures and of 5 object pictures (*see Appendix*). The three stimulus categories were tested in a Latin square design using the same set of stimulus items for each array.



TABLE 1. CATEGORY SPECIFICITY\*

| <i>Animals</i>        | <i>Flowers</i> | <i>Objects</i> |
|-----------------------|----------------|----------------|
| 86                    | 86             | 67             |
| n = 60, chance = 20%. |                |                |

\*Percentage correct score on a spoken word/picture-matching test (animals, flowers, objects).

*Results (1.10.84).* The percentage correct score for each category is given in Table 1. There was a significant overall effect of category ( $\chi^2$ , df2, = 9.95,  $P < 0.01$ ).

*Comment.* This result replicates our original observations in V.E.R. of impaired performance with the category of 'objects' as compared with flowers and animals. A larger set of stimulus items has been sampled (and for the flower category this necessitated using relatively low frequency items); nevertheless her level of performance was very satisfactory. These results strengthen the case for the dissociation of knowledge of common objects and living things.

#### *Experiment 2. Category specificity: foods, animals, objects*

The ability to point to a picture of a named food or animal was reported to be significantly worse than the ability to point to a named object in 3 patients recovering from herpes encephalitis (Warrington and Shallice, 1984). In this experiment our aim was not only to establish whether food was a preserved category for Y.O.T. as was the case for V.E.R. but also to establish whether Y.O.T., like V.E.R., was also sensitive to the duration of the RSI.

TABLE 2. CATEGORY SPECIFICITY AND 'RATE'\*

|                       | <i>Food</i> | <i>Animals</i> | <i>Objects</i> |
|-----------------------|-------------|----------------|----------------|
| 2 s RSI               | 93          | 85             | 63             |
| 5 s RSI               | 93          | 93             | 90             |
| n = 60, chance = 20%. |             |                |                |

\*Percentage correct on spoken word/picture-matching test for each category and at each Response-Stimulus Interval (RSI).

*Procedure.* The test stimuli consisted of three different picture arrays of 5 foods, 5 animals and 5 objects (see Appendix). The three stimulus categories were tested in a Latin square design using our standard 2 s RSI. Later on the same day this procedure was repeated using a slower 5 s interval.

*Results (29.9.84).* The percentage correct score for each category for each RSI is given in Table 2. There was a significant effect of category at the faster RSI, which is entirely attributable to her relatively impaired performance on the object category ( $\chi^2$ , df2, = 18.3,  $P < 0.001$ ). There was no category effect whatsoever with the slower RSI. The difference in her overall level of performance on the two occasions is entirely due to an increased score on the object category at the slower rate.

*Comment.* In this experiment we have confirmed our previous observations in

our patient, V.E.R., in so far as preservation of the food category has also been established in the context of a selective impairment in the object category. These findings contrasted with those of the cases with herpes encephalitis (Warrington and Shallice, 1984) provide strong evidence for a double dissociation between knowledge of objects on the one hand and knowledge of food and animals on the other. Not only is Y.O.T. similar to V.E.R. in showing a category effect, but she also shows a rate effect. From this we would infer that Y.O.T., like V.E.R., has difficulty in accessing semantic information rather than in the absolute loss or degradation of the semantic representation *per se*. This finding will be discussed in greater detail below.

*Experiment 3. Category specificity: foods, manipulable objects and large man-made objects*

Our aim in this experiment was to explore a major functional subdivision within the broad category 'objects'. Clinical observation suggested that Y.O.T. had particular difficulties in comprehending small manipulable objects as compared with large man-made objects. In this experiment we report our attempt to quantify this observation.

*Procedure.* The test stimuli consisted of three different picture arrays of 5 small manipulable objects, 5 large man-made objects, and 5 foods (see Appendix). The latter condition, using one of her preserved categories, was included as a baseline and for comparison with the two object conditions. The three stimulus categories were tested in a Latin square design.

*Results (1.10.84).* The percentage correct score for each of the three categories is given in Table 3. There was a significant overall effect of category which is

TABLE 3. CATEGORY SPECIFICITY\*

| <i>Foods</i> | <i>Large<br/>man-made<br/>objects</i> | <i>Manipulable<br/>objects</i> |
|--------------|---------------------------------------|--------------------------------|
| 83           | 78                                    | 58                             |

*n* = 60, chance = 20%

\*Percentage correct on spoken word/picture-matching test for each category (foods, large man-made objects, manipulable objects).

attributable to her relatively impaired performance on the small manipulable object category ( $\chi^2$ , *df*2, = 210.7,  $P < 0.01$ ).

*Comment.* Within the broad category of objects we have demonstrated significantly different levels of performance: one subclass that we have designated 'manipulable' objects is impaired as contrasted with the relative preservation of the subclass we have termed 'large man-made'. Y.O.T.'s comprehension of the latter category is at an equivalent level to that of foods, one of her categories of preserved comprehension. We will discuss the more theoretical implications of these observations below.

*Experiment 4. Fine-grain category specificity using an auditory/printed word matching task*

We have established (*see above*) that Y.O.T. was a phonological dyslexic with some preservation of printed word to picture matching. In this experiment we explore her ability to match a spoken-word to an array of written words. Using this technique enabled us to investigate a wide range of vocabulary without the constraints imposed by the limitations of pictorial material. Our aim in this experiment was to obtain evidence for a more fine-grained categorical organization of knowledge systems. We selected 16 diverse categories to include subcategories of objects, subcategories of foods and in addition a number of categories we had not previously tested.

*Procedure.* The test stimuli were selected from each of 16 Battig and Montague categories and consisted of two different 6-item arrays of printed words (*see Appendix*). Y.O.T. was required to match a spoken word to one of the 6 written words of the array. One array from each category was tested on 5.10.84 and the other array for each category on 6.10.84 in the order indicated in Table 4.

TABLE 4. FINE-GRAIN CATEGORY SPECIFICITY\*

| Category               | 1st | 2nd | Total ( $\bar{X}$ ) |
|------------------------|-----|-----|---------------------|
| Animals (3)            | 83  | 94  | 88                  |
| Occupations (10)       | 88  | 88  | 88                  |
| Vegetables (9)         | 83  | 83  | 83                  |
| Fabrics (4)            | 94  | 66  | 80                  |
| Accommodation (12)     | 72  | 83  | 77                  |
| Fruit (1)              | 72  | 77  | 75                  |
| Clothing (2)           | 83  | 50  | 66                  |
| Transport (11)         | 61  | 72  | 66                  |
| Colours (5)            | 66  | 56  | 61                  |
| Flowers (14)           | 77  | 38  | 58                  |
| Geographical (6)       | 56  | 56  | 56                  |
| Kitchen utensils (15)  | 44  | 50  | 47                  |
| Weather (13)           | 38  | 50  | 44                  |
| Office stationery (16) | 50  | 27  | 39                  |
| Furniture (7)          | 33  | 11  | 22                  |
| Parts of body (8)      | 17  | 22  | 19                  |

$n = 36$ , chance = 17%

\*Percentage correct on spoken word/written word matching test for each of 16 categories.  
Number in brackets indicates the order in which the category was tested.

*Results (5 and 6.10.84).* The percentage correct for each category on each occasion, together with the total percentage correct, is given in Table 4. The correlation (Spearman) between her scores for the two arrays of stimuli was 0.6 ( $P < 0.05$ ). Apart from the two categories on which she scored at an overall chance level (furniture and parts of the body), there was a clutch of categories for which her performance, although not error-free, was remarkably satisfactory (namely, animals, occupations, vegetables and materials) and a further group on which her scores were at an intermediary level (e.g., colours, geographical features, kitchen

utensils). There was an overall significant effect of category ( $\chi^2$ ,  $df15$ , = 108.7,  $P < 0.001$ ).

*Comment.* First, we have obtained evidence for category specific impairment and preservation using a spoken-word to written-word matching test. We would argue that these are reliable findings in so far as we replicated our first set of observations using a parallel set of test stimuli on a subsequent test session even though this necessitated using relatively low frequency words in some categories (e.g., flowers). Secondly, in general we have corroborated the broad category effects obtained in Experiments 1, 2 and 3 (with possibly two exceptions). Thirdly, we have probed a wider range of categories, some of which are not obviously a subset of either man-made objects or living things and foods. In these categories we have also obtained evidence of fractionation: thus her comprehension of occupations was remarkably preserved, whereas her comprehension of geographical features was by comparison weak.

#### *Experiment 5. Category specificity: proper nouns (8.10.84)*

In Experiment 4 we established that a spoken word to printed-word matching task produced replicable fine-grained category effects. Our aim in this experiment was to assess Y.O.T.'s comprehension of a number of verbal categories not hitherto investigated in order to obtain a reasonably comprehensive picture of her residual verbal vocabulary. Thus we assessed her proper noun vocabulary. The categories

TABLE 5. CATEGORY SPECIFICITY: PROPER NOUNS

| <i>Category</i>          | <i>Percentage correct</i> |
|--------------------------|---------------------------|
| Famous people (11)       | 100                       |
| Countries (1)            | 88                        |
| Cities (7)               | 88                        |
| Sports (4)               | 77                        |
| Emotions (8)             | 61                        |
| Units of time (9)        | 50                        |
| Parts of a house (5)     | 44                        |
| Girls' names (2)         | 38                        |
| Musical instruments (10) | 33                        |
| Academic subjects (3)    | 27                        |
| Surnames (12)            | 22                        |
| Boys' names (6)          | 17                        |

$n = 18$ , chance = 17%.

included were countries, cities and names of famous people (proper nouns with a unique referent) and familiar christian and surnames (proper nouns without a high probability unique referent). In addition some abstract word categories were tested and some further subcategories of objects that were not included in Experiment 4.

*Procedure.* The test stimuli consisted of 6-item arrays from each of 12 categories (see Appendix). Each category was tested in the order indicated in Table 5, using blocks of 18 trials for each category.

*Results (8.10.84).* The proportion correct for each category is given in Table 5.

There is an overall significant effect of category ( $\chi^2$ ,  $df11$ , = 65.3,  $P < 0.001$ ). The most striking finding is the remarkable preservation of her comprehension for the names of famous people and geographical place names as compared with the comprehension of familiar christian names and surnames for which her performance was no better than chance. Her comprehension of academic subjects was also at a chance level and her comprehension of the other abstract categories was at an intermediate level. Had it been possible to match word frequency familiarity for the items in the 'intermediate' categories, a more clear-cut result might have been observed. Of the other categories probed it is worth noting that her comprehension of parts of the house and musical instruments, a subclass of small man-made objects, was impaired.

*Comment.* First, her comprehension of proper nouns with a high probability unique referent was preserved and contrasts with her very poor comprehension of familiar proper nouns without a unique referent. The dissociation was clear-cut and occurred for three subclasses of each of these two types of proper nouns. This pattern of dissociation has not to our knowledge been observed previously and will be discussed below. Her comprehension of academic subjects was extremely poor and contrasts with what would appear to be a not dissimilar category, namely sports. Secondly, for Y.O.T. it appears as though her residual abstract word vocabulary is at an intermediate level and this case is therefore neutral with regard to the abstract/concrete dichotomy.

#### *Experiment 6a. Effects of semantic similarity using spoken-word/picture matching*

Our aim in this experiment was to explore the effect of semantic similarity between items in an array for Y.O.T.'s residual comprehension abilities, since we have previously reported the importance of such effects using matching to sample paradigms. Five subsets were selected from the broad 'object' category, a category we have already established was poorly comprehended. In addition the impaired category, parts of the body, was included. For comparison we probed semantic similarity effects within five subsets from her preserved categories (i.e., countries, famous people, famous buildings, occupations and transport) and one additional category, namely geographical features.

*Procedure.* The test stimuli consisted of arrays of 6 pictures from each of six of her impaired subsets and six of her preserved subsets. Each of the two sets of 36 stimulus items were tested under conditions of 'close' and 'distant' semantic similarity. In the 'close' semantic condition all 6 items of the array were from the same impaired subset (e.g., book, key, pen, pencil, envelope, telephone) or from one of the same spared subset (e.g., famous people) (*see* Table 6). In the 'distant' semantic condition the arrays consisted of 1 item from each of the six 'impaired' (e.g., pencil, chair, door, foot, hat, pen) or six 'preserved' categories (India, Napoleon, cliff, Parthenon, train and dentist) (*see* Appendix). Y.O.T. was tested in blocks of 18 trials for each array. The order of presentation of the four types was: (1)

TABLE 6. CATEGORY SPECIFICITY AND SEMANTIC DISTANCE\*

| <i>Impaired</i>     |              |                | <i>Preserved</i> |              |                |
|---------------------|--------------|----------------|------------------|--------------|----------------|
| <i>Category</i>     | <i>Close</i> | <i>Distant</i> | <i>Category</i>  | <i>Close</i> | <i>Distant</i> |
| Office stationery   | 33           | 78             | Famous people    | 100          | 94             |
| Household           | 50           | 67             | Occupations      | 100          | 94             |
| Clothes             | 56           | 94             | Geographical     | 67           | 100            |
| Kitchen utensils    | 83           | 83             | Transport        | 83           | 94             |
| Furniture           | 39           | 100            | Buildings        | 100          | 100            |
| Parts of body       | 22           | 56             | Countries        | 100          | 100            |
| Total ( $\bar{X}$ ) | 47           | 79             |                  | 92           | 97             |

n = 18, chance = 17%

\*Percentage correct on spoken word/picture-matching test for each category of object in 'close' and in 'distant' semantic arrays.

close/impaired, (2) close/preserved, (3) distant/impaired, (4) distant/preserved; this order was maintained until all stimuli had been tested.

*Results (10.10.84).* The percentage correct for each category for each semantic similarity condition is given in Table 6. Her performance is at ceiling on those categories previously shown to be preserved and therefore the effect of semantic similarity could not be examined. There is a highly significant effect of semantic similarity within the impaired category sets (binomial  $x=0$ ,  $P=0.02$ ). It is worth noting that her worst performance in both the 'close' and 'distant' conditions was for parts of the body, the category most dissimilar to the other five selected impaired categories!

*Comment.* First, we have replicated and extended our previous documentation of semantic similarity effects. Secondly, it is clear that her performance on her preserved and impaired subsets is in excellent accord with the results obtained in Experiment 4 although a different set of items was tested. In addition, a previously untested subclass of referential proper nouns, famous buildings and monuments was included and her performance was error-free even in the 'close' semantic condition. The significance of the effect of semantic similarity within the impaired subsets will be discussed below.

#### *Experiment 6b. Effects of semantic similarity using written-word/picture matching*

In the previous experiment we used a spoken-word to picture matching task to examine semantic similarity effects. In this experiment our aim was to replicate the 'close' and 'distant' effects within Y.O.T.'s impaired subsets, using a written word to picture matching task.

*Procedure.* The test stimuli consisted of the same six arrays of pictures that were used in Experiment 6 to probe her comprehension of the impaired subsets and a written-word stimulus was substituted for the spoken word in the matching task. The close and distant conditions were identical to those in Experiment 6, and the

12 blocks were tested using an ABBA design with respect to the 'close' and 'distant' conditions.

*Results.* The percentage correct for each category for each condition are given in Table 7. With one exception, her performance is above chance for all the categories in the 'close' condition (parts of the house). In the 'distant' condition her performance on each category tested was superior to when tested in the close condition. The difference in her overall level of performance between the close and distant conditions is significant (binomial  $x = 0$ ,  $P = 0.02$ ).

TABLE 7. CATEGORY SPECIFICITY AND SEMANTIC DISTANCE\*

| Category            | Close | Distant |
|---------------------|-------|---------|
| Office stationery   | 44    | 66      |
| Household           | 22    | 61      |
| Clothes             | 61    | 66      |
| Kitchen utensils    | 44    | 72      |
| Furniture           | 39    | 56      |
| Parts of body       | 50    | 77      |
| Total ( $\bar{X}$ ) | 44    | 68      |

$n = 18$ , chance = 17%

\*Percentage correct on written word/picture-matching test for each category in the 'close' and 'distant' semantic distance conditions.

*Comment.* Her overall level of performance on this test is very comparable to that observed when the arrays were tested using the spoken-word to picture matching. Significant effects of semantic similarity have again been obtained. With the exception of the parts of the body category all the stimulus items could be subsumed within the class of man-made objects. Yet within and between the subsets very clear semantic similarity effects have been obtained. We would argue that superordinate knowledge of these subcategories could not account entirely for these findings and we will consider below an alternative account in terms of refractoriness within the semantic system.

### General analysis

*Consistency analysis.* The overall proportion of correct responses for each category or condition tested could have arisen due to consistent responding (either consistently correct or consistently incorrect) to particular items. Alternatively her incorrect response could be randomly distributed taking into account her overall error rate. The sets of data from Experiments 2 and 3 on which her scores were neither at floor or at ceiling (i.e.,  $N(p)$  and  $N(q) > 1$ ) were analysed for response consistency using the binomial dispersion test (Wetherill, 1972). This is sensitive to those instances on which her performance on individual items was either consistently good or bad. In both instances her performance conformed very closely to the binomial distribution ( $\chi^2$ ,  $df14$ , = 12.6,  $P > 0.5$ ;  $\chi^2$ ,  $df14$ , = 9.56,  $P > 0.7$ ,

respectively) indicating significant variability rather than consistency in her performance on individual items.

*Serial trial analysis.* In Experiments 2 and 3, each of 45 stimulus items was probed 4 times. Comparing Y.O.T.'s first response to an item with her second response to the same item, there was a significant decrement in her performance in both experiments such that her second response was likely to be less accurate than her first (binomial test,  $n=13$ ,  $x=2$ ,  $P=0.01$  and  $n=10$ ,  $x=1$ ,  $P=0.01$ , respectively). In Experiment 4 in which each of 196 stimuli were probed 3 times, there was again a significant decrement between her first and second response to individual items ( $n=66$ ,  $x=22$ ,  $P=0.005$ ). In Experiment 5 in which 72 items were probed 3 times, there was not a significant serial trial effect ( $n=22$ ,  $x=11$ ,  $P=0.3$ ). Finally, in Experiments 6 and 7, considering only her performance on those six categories designated 'impaired' tested in the 'close' condition, there was a significant serial trial effect in the former ( $n=14$ ,  $x=2$ ,  $P=0.006$ ) but not in the latter ( $n=18$ ,  $x=7$ ,  $P=0.024$ ). Thus in 4 of these 6 experiments (Experiment 1 was omitted from this analysis as only 15 stimulus items were probed) there is a decrement in her performance with repeated testing.

## DISCUSSION

In this series of experiments we have documented the residual comprehension abilities of a patient Y.O.T. who had a severe global dysphasia such that her capacity for comprehension and production of propositional speech appeared to be virtually absent. Nevertheless, using matching to sample techniques, we were able to document islands of preserved comprehension. The main theme of these experiments has been the investigation of her comprehension of a wide range of verbal categories. Before discussing the implications of our evidence of fine-grain categorical deficits, we will consider briefly two issues: first, whether her deficit should be construed as one of 'degradation' of the semantic representation or in procedures for accessing them and secondly, the question of modality specificity.

We have characterized an *access* deficit in terms of inconsistency in the availability of a particular representation over time. It differs from a *degradation* deficit in which the central representation itself appears to be damaged, and in these cases response consistency may be observed (Coughlan and Warrington, 1981). Y.O.T., like our previous patient V.E.R., whom we identified as a semantic access dysphasic, showed inconsistent performance on items within categories for which her overall performance was significantly above chance. More crucially she showed clear-cut *rate* effects in that the response-stimulus interval (RSI) was a significant determinant of her performance. In addition, as with V.E.R., effects of serial position were obtained within her impaired categories, thus her performance deteriorated between the first and second presentation of an item. Her inconsistency could therefore not be accounted for in terms of any simple 'random walk' through a set of generally or specifically degraded semantic representations. We would therefore classify



Y.O.T.'s comprehension deficit as being due to an inability to *access* central semantic representations of concepts.

We have previously advanced the concept of 'refractoriness' to account for this constellation of deficits and in particular the observation that an access deficit could also be category specific. As with V.E.R., we would suggest that Y.O.T.'s semantic knowledge base was liable to become refractory following activation. In this regard the semantic distance effects are consistent with a gradient of spreading refractoriness. Indeed our present data provide stronger evidence that these deleterious effects of activation affect not only the processing of a single semantic representation but extend to those that are semantically related. Thus under conditions where knowledge of the superordinate concept would be of no obvious benefit, we still obtained clear effects of semantic distance. Her performance on arrays of closely related items (but note these were neither perceptually nor semantically confusable) was very significantly impaired. This contrasted with her superior ability to recognize the same items when they were probed in semantically distant arrays.

Whether in this instance a particular set of 'close' semantic entries became refractory or whether it was the particular procedures required to access such representations that became refractory remains an open question. Such possibilities are not exhaustive, neither are they mutually exclusive and indeed in some formulations might be considered as identical. Semantic distance effects are clearly compatible with either possibility. It is of interest to note that analagous category specific refractory effects have been reported in normal subjects (e.g., Tipper, 1985).

It has been suggested that the semantic knowledge systems may have modality specific processing components (e.g., Warrington, 1975; Beauvois, 1982; Warrington and Shallice, 1984; McCarthy and Warrington, 1986). The observations that the comprehension deficits within one modality are not necessarily mirrored by those in other modalities (i.e., there may be a mismatch between verbal and visual comprehension) have been adduced as evidence for this position.

Our clinical assessment established that Y.O.T. had a visual recognition deficit, a profound auditory verbal comprehension deficit and was dyslexic. It was necessary to use matching to sample techniques to investigate her residual comprehension abilities. This inevitably involves two domains of information processing and therefore precludes any viable evaluation of the relative contribution of each mode of presentation. In particular, on the basis of the evidence we have presented here it would not be appropriate to discuss the problem of the relationship between say verbal semantic knowledge and visual semantic knowledge nor between the different modes of verbal processing (e.g., comprehension of the spoken word as compared with the written word). Our discussion will be cast in very general terms since the evidence in this case is neutral with regard to the interrelationship of verbal and visual semantic processing. The possibilities include complete autonomy of each system (e.g., Warrington and Shallice, 1984; Beauvois, 1982) and temporary inter-

dependence during acquisition (Clark, 1973), through to single unitary systems (Allport and Funnell, 1981; Ratcliff and Newcombe, 1982).

### *Category specificity*

In each of these experiments we have obtained evidence for the relative impairment and relative preservation of the comprehension of a number of semantic categories. These included a number of categories previously investigated and in addition some which have not hitherto been explored. Similar category effects were observed on each of the three types of matching task, and the pattern of relative preservation and relative impairment was remarkably consistent across experiments. There are two major aspects of this evidence of category specificity that merit further discussion. First, does a 'physical/functional' typology account adequately for the pattern of dissociations within Y.O.T.'s residual concrete word vocabulary. Secondly, what are the implications of the fractionation within her proper noun vocabulary, for the organization of knowledge systems?

To recapitulate, we have previously argued that the identification of man-made objects crucially depends on precise functional specifications whereas for the identification of living things and food physical features provide the major defining characteristics. The physical/functional dichotomy was introduced as a refinement of the older animate/inanimate distinction in order to account for certain anomalies in the patterns of preserved and impaired comprehension observed in patients with impairments of their concrete word vocabulary. Thus, specifically, a dissociation between the animate and inanimate concepts was documented in J.B.R. (Warrington and Shallice, 1984). However, his comprehension of fabrics, an inanimate category, was extremely poor whereas his comprehension of body parts (surely animate) was very good. Thus while the animate/inanimate distinction fails the physical/functional distinction appeared to be fairly satisfactory.

This physical/functional typology certainly provides a first approximation as an account of Y.O.T.'s pattern of preserved and impaired comprehension. The broad category effects were opposite to those of J.B.R. (and the 3 other similar cases). This replicates our previously reported dissociation in V.E.R. in that animals, plants and foods were relatively preserved compared with objects (Warrington and McCarthy, 1983). Moreover Y.O.T.'s performance on those particular categories that first led to the introduction of a physical/functional typology, namely 'body parts' and 'fabrics' was a mirror image of J.B.R.'s. Thus her comprehension of fabric names was remarkably good whereas her comprehension of body part names was particularly bad. This latter result appears to be particularly robust in so far as it was obtained using all three types of matching task.

Nevertheless, the present data presents a number of problems for this physical/functional formulation. We have evidence of a fractionation within the broad category of man-made objects that would hardly be predicted within such a framework. We were alerted by the clinical description by Yamadori and Albert (1973) of a patient with particular difficulty in comprehending indoor objects as

compared with outdoor objects, and tested Y.O.T. with items from these categories. We obtained evidence for a selective impairment in her comprehension of small manipulable objects, her comprehension of large 'outdoor' man-made objects being as competent as that of one of her major preserved 'physical' categories, namely foods. Further evidence for this dissociation was obtained using arrays of 'close' semantic coordinates. Thus, for example, comprehension of types of buildings and kinds of transport were relatively preserved whereas comprehension of household furniture and office equipment was impaired. On the basis of this dissociation in Y.O.T.'s performance, we would reject any simplistic account of her verbal comprehension abilities cast purely in terms of the predominance of processing either physical or functional attributes. Boats and houses, for example, are clearly comprehended in terms of their functional core properties, at least to the same extent as pencils and chairs.

Before discussing the more theoretical issues raised by these observations we shall consider briefly the implications of the other major dissociation in Y.O.T.'s comprehension vocabulary, namely the selective preservation and selective impairment within her proper name vocabulary.

We observed, first, that she was able to point to a named famous person or building in an array of pictures; secondly, that her performance was equally good with similar stimuli presented in a written array and, thirdly, she also had no difficulty in comprehending the names of countries and counties. By contrast she scored at a chance level in pointing to common surnames, boys' names and girls' names. These observations could be considered as indicative of a potential double dissociation between well-known people's names and well-known names of people, since a patient is on record who had a selective deficit in retrieving well-known people's names but no difficulty in generating boys' and girls' names (McKenna and Warrington, 1980).

The distinction between those proper names that are of a distinct and unique individual (e.g., Picasso) and those that do not have a high probability common referent has been anticipated on theoretical grounds (Miller and Johnson-Laird, 1976). All proper names clearly have referential and pragmatic roles. However, only in the case of a high probability or well-known referent do they have an unambiguous meaning which is independent of context. Take the example 'Michael painted a ceiling' and 'Michelangelo painted a ceiling'; the meaning conveyed by the two sentences is very different. In the former case the proper name fulfills a somewhat restricted generic role, in the latter the referent is quite specific. For Y.O.T. this distinction is borne out empirically at the level of the single word; Mozart and India appear to be comprehended whereas Anne and Jones are not.

### *Theoretical considerations*

We have both replicated and extended previously described dissociations between categories of verbal knowledge. There appears to be increasing evidence for a fine-grain categorical organization of knowledge systems (e.g., Warrington and Shallice,

1984; Hart *et al.*, 1985). How can these multiple dissociations be incorporated into a principled account of systems achieving comprehension of meaningful stimuli? We would suggest that it may be appropriate to return to the classical concept of associative agnosia — which was first expounded in detail by Lissauer (1890) and whose ideas were in turn drawn from the English school of empiricist philosophy. The core concept for Lissauer was that meaning is acquired through the linkage of the output of perceptual processing systems with memory 'images' laid down in the brain through other sense modalities. To illustrate his position he gives the following example of recognizing a violin.

'With the violin's image there are connected a number of recollections which concern its name, its sound, its image. The sound of the instrument, the sensations and tactile experience which go with its handling. In addition there may be the optical image of a violinist in his characteristic pose. It is only when these associations between the percept of the instrument and the above-mentioned recollections occur promptly in consciousness that one is enabled to interpret the object as a musical instrument and differentiate it from other instruments and generally to categorise it. If, however, this association is delayed or disrupted through some pathological process then even if the image of the violin is perceived, however precisely, there are no associations with prior experiences and recognition is therefore not possible.'

In this example, it is clear that Lissauer wished to emphasize the relevant contribution of various modalities of experience towards the acquisition of meaning (applied in conjunction with or following a full perceptual description). We wish to extend the associationist framework and to speculate that the relative 'importance' or 'weighting' values of different channels of sensory/motor evidence could possibly form the basis of category specificity in the brain. By 'weighting' value we mean that the information from each of the relevant channels will make a different quantitative contribution to the overall computational processes involved in the initial acquisition and resultant comprehension of meaningful stimuli. To anticipate, we shall argue that the end product of such processing is a categorically organized knowledge base.

We shall attempt to elaborate this conceptualization with reference to the differentiation of several minimal pairs. We will adopt as a working assumption that the processes involved in differentiation between two similar members of a class are a prerequisite not only for their acquisition but also for subsequent use. Consider the differentiation of 2 animals (a sheep and a goat) as compared with 2 foods (butter and cheese). In the former instance, visual information is the most important sense modality; however, in the latter, taste information would appear to be more important than visual information. The relative salience of each of the sense modalities is clearly different in these instances of categories comprehended in terms of their sensory attributes. In addition, however, the weighting values from sensory/motor channels of information may be of significance in the differentiation of 2 similar man-made objects. For example, visual information is clearly relevant

for the differentiation of, say, a chair and a stool but much less so in the case of a shirt and a jacket. Of course, knowledge of function itself may be a product of a more abstract or more schematized representations based (at least during acquisition) on sensory/motor information.

So far this account is merely a development of the earlier broad class distinction between the predominance of physical or functional attributes for the comprehension of meaning. However, we wish to argue that this framework can be elaborated to account for fine-grain categorical dissociations. These may arise not only as a consequence of differing weighting values between information from each of the major sensory/motor modalities, but also as a consequence of different weighting values on more specialized channels within each modality. It is becoming clear that for each of the major modalities there is differentiation into a number of components. To take the example of visual functions, colour, shape, motion and location are known to be separable both physiologically, anatomically and psychologically at very early stages of information processing (e.g., Zeki, 1980; Duncan, 1984; Livingstone and Hubel, 1984). It seems not implausible to suggest that this early segregation may have concomitants for later stages of cognitive analysis and that the evidence provided by or derived from such functions (i.e., channels), may interact differentially with information from other sources.

Consider first the recently reported selective impairment in naming fruit and vegetables, surely an example of fine-grain categorical dissociation. The differentiation of two vegetables (e.g., cabbage and cauliflower) or two fruits (e.g. blackberry and raspberry) can be compared with the differentiation of a closely related category, namely 2 flowers (e.g., a tulip and a carnation). In the former instance, visual information clearly has a high weighting. In addition, within the visual channels, *colour* rather than *shape*, is the critical attribute. For flowers, visual information is once again the dominant sensory channel but *shape* rather than *colour* information is crucial.

Turning now to the fine-grain dissociation between small manipulable objects and large man-made objects which we have documented in Y.O.T., although both classes of object have a functional core meaning, the weightings on sensory/motor information may be very different in the two cases. The differentiation of say a key and a pen as contrasted with a plane and a helicopter require very different contributions from each of the major information channels. Visual shape information might have lower priority for the former but be highly salient for the latter. Perhaps more relevant for differentiating between man-made objects is the importance of somatosensory information and information derived from actions. For small manipulable objects the information derived from fine distal arm movements is highly salient but clearly much less so for large man-made objects. It is of some interest that this distinction within the broad class of man-made objects had been anticipated by Konorski (1967) and Gilinsky (1984) within a somewhat related theoretical framework.

Can this account of relative weighting values of different channels of sen-

sory/motor evidence also be applied to those concepts which are not obviously encompassed by the broad physical/functional distinction? It is clearly compatible with the double dissociation observed between impairments of abstract and concrete verbal vocabularies. The contributions of such channels for comprehension of abstract concepts is likely to be of minor importance. Similarly, there is likely to be a high weighting value on motor channels for the comprehension of action verbs. Whether this approach, however, is equally applicable to the dissociation observed in Y.O.T.'s proper name vocabulary is more problematical. Well-known names differ from other items in the concrete word vocabulary perhaps only in that they refer to a unique and invariant concept. As with other categories within the concrete domain the relative weighting values from each of the sensory/motor channels will be salient. By contrast, well-known names of people do not refer to a unique and invariant concept. It would therefore seem likely that their semantic representation will depend on highly complex interactions between multiple information channels.

The present account is intentionally a general one that deals with the initial stages of semantic analysis. These we suggest are best described in terms of strict categorical organization. At the same time we do not wish to deny that there may be other levels of cognitive procedures mediating comprehension (e.g., associative searches) that are based on other principles. It has nevertheless the advantage of systematizing some of the apparently arbitrary examples of category specificity within the concrete noun vocabulary that are observed following lesions to the brain. It is possible that the patterns of fractionation which are observed reflect the topographical or physiological organization of neural systems that are involved in knowledge processing. Indeed, on such an account, category specific deficits may be an emergent property of the acquisition of competence in such processing. Our current perspectives have much in common with contemporary computational connectionist models of knowledge processing in which representations are computed on the basis of weighted entries in parallel distributed processing systems (e.g., Hinton 1981; Ballard, 1986). It is perhaps not overoptimistic to suggest that an approach based on such models may not only be able to provide a rational basis for category specific effects but it is possible that they may also be able to predict as yet unrecorded dissociations.

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# APPENDIX

## Experiment 1 stimuli

| Flowers   | Animals | Objects  |
|-----------|---------|----------|
| Nettles   | Tiger   | Scissors |
| Buttercup | Camel   | Steps    |
| Thistle   | Monkey  | Fork     |
| Rose      | Giraffe | Mop      |
| Daffodil  | Zebra   | Hammer   |

## Experiment 2 stimuli

| Foods        | Animals     | Objects      |
|--------------|-------------|--------------|
| Mushrooms    | Lion        | Present      |
| Sprouts      | Duck        | Crayons      |
| Lemons       | Chicken     | Cotton       |
| Buns         | Butterflies | Bicycle      |
| Jam          | Elephant    | Camera       |
| Onions       | Dog         | Rollerskates |
| Beans        | Horse       | Umbrella     |
| Lolly        | Sheep       | Clothes pegs |
| Steak        | Bird        | Wheelbarrow  |
| Strawberries | Fish        | Mirror       |
| Milk         | Cat         | Pram         |
| Soup         | Rabbit      | Buttons      |
| Ice cream    | Cow         | Balloons     |
| Lettuce      | Frog        | Swing        |
| Pear         | Swan        | Paints       |

## Experiment 3 stimuli

| Foods       | Indoor objects | Outdoor objects |
|-------------|----------------|-----------------|
| Cherries    | Chair          | Aeroplane       |
| Grapes      | Fork           | Ship            |
| Corn        | Hairdryer      | Lorry           |
| Orange      | Desk           | Gate            |
| Melon       | Paper clips    | Harvester       |
| Dates       | Cup            | Bus             |
| Apples      | Pencils        | Tank            |
| Banana      | Lamp           | Train           |
| Peas        | Record         | House           |
| Tomato      | Sewing machine | Fence           |
| Peaches     | Belt           | Windmill        |
| Cucumber    | Clock          | Pier            |
| Carrots     | Cushion        | Bridge          |
| Grapefruit  | Shoe           | Tanker          |
| Cauliflower | Kettle         | Shed            |

## Experiment 4 stimuli

| Fruits | Clothes | Animals | Materials |
|--------|---------|---------|-----------|
| Grape  | Jacket  | Horse   | Wool      |
| Banana | Skirt   | Tiger   | Cotton    |
| Orange | Socks   | Cat     | Linen     |
| Cherry | Cap     | Cow     | Nylon     |
| Pear   | Blouse  | Dog     | Velvet    |
| Apple  | Scarf   | Pig     | Silk      |



|            |              |                 |                |
|------------|--------------|-----------------|----------------|
| Lemon      | Tie          | Rat             | Satin          |
| Peach      | Hat          | Donkey          | Denim          |
| Apricot    | Dress        | Bear            | Canvas         |
| Raspberry  | Coat         | Camel           | Corduroy       |
| Plum       | Glove        | Sheep           | Rayon          |
| Melon      | Shoe         | Goat            | Tweed          |
|            |              |                 |                |
| Colours    | Geographical | Furniture       | Parts of body  |
| Blue       | Features     | Table           | Elbow          |
| Yellow     | Mountain     | Rug             | Mouth          |
| Purple     | River        | Chair           | Foot           |
| Green      | Cave         | Bed             | Nose           |
| Brown      | Lake         | Bench           | Eye            |
| Red        | Valley       | Stool           | Arms           |
|            | Cliff        |                 |                |
| Black      | Hill         | Lamp            | Ear            |
| White      | Island       | Carpet          | Knee           |
| Orange     | Ocean        | Sofa            | Shoulders      |
| Grey       | Beach        | Desk            | Chin           |
| Pink       | Forest       | Wardrobe        | Finger         |
| Beige      | Desert       | Curtains        | Leg            |
|            |              |                 |                |
| Vegetables | Occupations  | Transport       | Accommodation  |
| Carrot     | Nurse        | Aeroplane       | Cottage        |
| Onion      | Teacher      | Van             | Palace         |
| Tomato     | Dentist      | Car             | Cabin          |
| Lettuce    | Doctor       | Train           | House          |
| Peas       | Engineer     | Ship            | Tent           |
| Turnip     | Baker        | Bus             | Hotel          |
| Potato     | Lawyer       | Taxi            | Flat           |
| Spinach    | Grocer       | Motorbike       | Caravan        |
| Sprouts    | Typist       | Boat            | Castle         |
| Cucumber   | Salesman     | Helicopter      | Bungalow       |
| Leeks      | Carpenter    | Truck           | Mansion        |
| Cabbage    | Plumber      | Coach           | Hut            |
|            |              |                 |                |
| Weather    | Flowers      | Kitchen objects | Office objects |
| Snow       | Daisy        | Saucer          | Envelope       |
| Gale       | Tulip        | Pan             | Brush          |
| Wind       | Rose         | Spoon           | Pen            |
| Drought    | Violet       | Bowl            | Coin           |
| Rain       | Crocus       | Dish            | Book           |
| Thunder    | Poppy        | Knife           | Scissors       |
| Flood      | Daffodil     | Fork            | Rubber         |
| Fog        | Iris         | Whisk           | Ashtray        |
| Lightning  | Lily         | Jug             | Papers         |
| Sunshine   | Orchid       | Glass           | Clock          |
| Shower     | Carnation    | Cup             | Ruler          |
| Storm      | Geranium     | Plate           | Purse          |

*Experiment 5 stimuli*

|           |         |               |              |
|-----------|---------|---------------|--------------|
| Countries | Cities  | Famous people | Girls' names |
| Germany   | Dublin  | Churchill     | Anne         |
| Russia    | Glasgow | Hitler        | Susan        |
| Canada    | Hull    | Napoleon      | Sally        |
| England   | Cardiff | Picasso       | Jane         |
| France    | Bristol | Dickens       | Elizabeth    |
| Italy     | London  | Mozart        | Mary         |

|                              |                  |               |                       |
|------------------------------|------------------|---------------|-----------------------|
| Boys' names                  | Surnames         | Subjects      | Sports                |
| David                        | Jones            | History       | Boxing                |
| Peter                        | Thompson         | Geography     | Golf                  |
| John                         | Williams         | Chemistry     | Swimming              |
| Richard                      | Baxter           | Biology       | Football              |
| Steven                       | Smith            | Maths         | Skiing                |
| Tom                          | Jackson          | Physics       | Tennis                |
| Parts of house               | Emotions         | Units of time | Musical instruments   |
| Ceiling                      | Happy            | Day           | Piano                 |
| Door                         | Tired            | Minute        | Drum                  |
| Wall                         | Greedy           | Month         | Flute                 |
| Window                       | Afraid           | Second        | Trumpet               |
| Roof                         | Angry            | Year          | Guitar                |
| Floor                        | Sad              | Hour          | Violin                |
| <i>Experiment 6a stimuli</i> |                  |               |                       |
| Office stationery            | People's names   | Furniture     | Occupations           |
| Book                         | Napoleon         | Desk          | Telephonist           |
| Key                          | Hitler           | Sofa          | Nurse                 |
| Pen                          | Victoria         | Chair         | Dentist               |
| Envelope                     | Gandhi           | Lamp          | Chauffeur             |
| Telephone                    | Henry VIII       | Table         | Artist                |
| Pencil                       | Shakespeare      | Bed           | Doctor                |
| Buildings                    | Kitchen utensils | Countries     | Parts of body         |
| Parthenon                    | Bowl             | Scotland      | Foot                  |
| Westminster                  | Fork             | France        | Arm                   |
| Eros                         | Bottle           | India         | Thumb                 |
| Eiffel Tower                 | Glass            | Wales         | Leg                   |
| Taj Mahal                    | Pan              | Germany       | Ear                   |
| Kremlin                      | Jug              | Spain         | Hand                  |
| Clothes                      | Parts of house   | Transport     | Geographical features |
| Shoe                         | Chimney          | Aeroplane     | Volcano               |
| Dress                        | Fireplace        | Lorry         | Valley                |
| Jersey                       | Stairs           | Boat          | Mountain              |
| Skirt                        | Door             | Car           | Cliff                 |
| Hat                          | Window           | Bus           | Dam                   |
| Belt                         | Roof             | Train         | River                 |

# T CELL SUBSETS IN MULTIPLE SCLEROSIS

## GRADIENTS AT PLAQUE BORDERS AND DIFFERENCES IN NONPLAQUE REGIONS

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### SUMMARY

This report provides a quantitative analysis of the distribution of helper-inducer T cells (H-I, LEU3A+) and cytotoxic-suppressor T cells (C-S, OKT8+) performed in a standardized fashion on material from 10 cases of multiple sclerosis. Particular attention was paid to cells at the plaque edge and to normal appearing white matter adjacent to plaques. Numbers of both the C-S and the H-I subset peaked directly at the edges of plaques, whether histopathologically active or inactive ( $P < 0.01$ ). Normal appearing areas outside active plaques had fewer C-S cells than equivalent areas outside inactive plaques ( $P < 0.05$ ). A study of three whole plaques showed that the sum of the two T cell subsets was significantly greater than the number of cells bearing the pan-T cell marker in two plaques and in two border regions.

The present results support a crucial role for the balance of T cell subsets in the evolution of plaque margins. When taken together with similar findings in experimental allergic encephalomyelitis, they suggest that helper-inducer cell dominance at the border is necessary for plaque expansion while C-S dominance in non plaque areas is associated with controlled disease. In addition, they suggest either modulation of the OKT3 surface antigen or the presence of a non-T cell bearing OKT8 in association with the site of histopathological change.

### INTRODUCTION

Over the last five to ten years there has been increasing evidence that host immune mechanisms play a role in the expression and progression of multiple sclerosis (MS). The nature of this involvement, however, has remained elusive. Strong evidence for changes in immune function associated with MS progression was first presented by Antel *et al.* (1979). They demonstrated a reduction of Con A-inducible T cell suppression in mononuclear cells from the blood of MS patients during exacerbation. Subsequent studies showed an association between the expression of

clinical MS and a decrease in the ratio of peripheral cytotoxic-suppressor (C-S) cells to helper-inducer (H-I) cells (Reinherz *et al.*, 1980; Bach *et al.*, 1980; Compston, 1983; Weiner *et al.*, 1984). Although the relationship between a drop in peripheral C-S cells and acute MS has been challenged, substantial evidence for this associated change remains in chronic-progressive disease (Paty *et al.*, 1984). Others have shown that as the number of T cells in the CSF increases, the percentage of C-S cells decreases in chronic-progressive MS (Hommes and Brinkman, 1984). These studies support T cell involvement in MS but they do not describe the patterns of infiltration of the target organ crucial to our understanding of the disease process.

In one study (Traugott *et al.*, 1983), T cells and macrophages were found inside plaques in acute MS while in chronic active MS, H-I cells penetrated the myelinated parenchyma with C-S cells confined to the lesion edge. In a previous quantitative study (Booss *et al.*, 1983), we showed that both T cell subsets were present in the normal appearing parenchyma and in both histopathologically active and inactive plaques. C-S cells were more numerous than H-I cells. Hauser *et al.* (1986) reported a similar distribution of T cells in the parenchyma and in regions of perivascular cuffing with an overrepresentation of C-S cells over H-I cells and also numerous Ia+ macrophages. One of the findings in a study of Woodroffe *et al.* (1986) was that the C-S preponderance was associated with widespread staining for class I MHC antigen. In addition, our studies (Booss *et al.*, 1983) showed that cells bearing the C-S subset marker outnumbered those bearing the pan-T cell marker in CNS sections containing MS plaques.

The plaque edge in established lesions may be the locus for immune interactions which control lesion progression. Previous reports have compared T cell subsets on the edge with plaque and nonplaque regions (Traugott *et al.*, 1983; Hauser *et al.*, 1986), but no studies of the gradients across the edge have been reported. We now report the first detailed quantitative study of the gradients of T cell subsets in the region traversing the plaque edge. We have also examined the distribution of T cell subsets in normal appearing white matter and differences in this distribution associated with adjacent plaque activity.

## MATERIALS AND METHODS

### *Tissue preparation and staining methods*

As previously reported, material for study was obtained from the UK and from the National Neurological Specimen Bank in the United States (Booss *et al.*, 1983). For the present study, CNS material from 10 cases (17 sections) were studied. Tissues from the UK were processed fresh while tissues from the National Neurological Specimen Bank were received frozen. Sections were cut with a cryostat ( $-20^{\circ}\text{C}$ ) at 10 to 12  $\mu\text{m}$  thickness, mounted on gelatin coated slides, and fixed in acetone for 10 min. All sections were brought to room temperature and washed with TRIS buffer (pH 7.4) and were treated with monoclonal antibodies diluted 1:5 or 1:10 in TRIS buffer in accordance with manufacturers recommendations. Serial sections were treated with LEU3A antibodies (Becton Dickson) against helper-inducer subset antigen, OKT8 antibodies (Ortho Diagnostics) against the cytotoxic-suppressor subset antigen, and OKT3 antibodies (Ortho Diagnostics) against the pan-T cell antigen. After incubation for 45 min in a humidified atmosphere, the sections were washed and

exposed to peroxidase conjugated rabbit antibody against mouse immunoglobulin (Dako) for 30 min and washed again before treatment with diaminobenzidine (60 mg/100 ml in TRIS buffer) with one drop of  $H_2O_2$  for 5 min. Sections were then washed in water, lightly counterstained with haematoxylin blue, dehydrated, cleared, and mounted. Separate sections from each series were also stained with a modified haematoxylin stain and oil red O so that the activity of the plaque could be assessed. The haematoxylin stain demonstrated the boundary and the cellularity of the lesion whereas the oil red O stained showed phagocytic cells laden with the products of myelin breakdown. Stained specimens were scanned at intermediate power so that the exact edge could be marked.

Fresh frozen acetone-fixed sections of tonsil were processed in parallel with the CNS sections when reactions were carried out with each antibody.

#### *Method of counting of the border region*

Fifteen sections from 9 cases which had visible intact plaque borders were selected for analysis. The borders of plaques stained with the LEU3A and OKT8 markers were carefully defined by comparing them to the sections stained with modified haematoxylin. Cells positively stained with each antibody were counted in square grids that were each circumscribed by one high power field ( $\times 400$ ). Data were recorded as the number of positively stained cells within a high power field grid. One field was centred on the border and the number of positive cells was recorded. Three fields into and 3 fields away from the plaque were also counted. Another field, centred adjacent to the first border field, was then centred on the border and the counting process into and away from the plaque was performed. This was repeated up to six times to produce a series of 7 field vectors for each plaque studied (fig. 1A, B). Equivalent areas of the border were tabulated for each of the two antibodies. To estimate the number of positive cells at each of the 7 distance fields we had to first take into account large differences due to the variable number of positive cells in a section. This regression problem

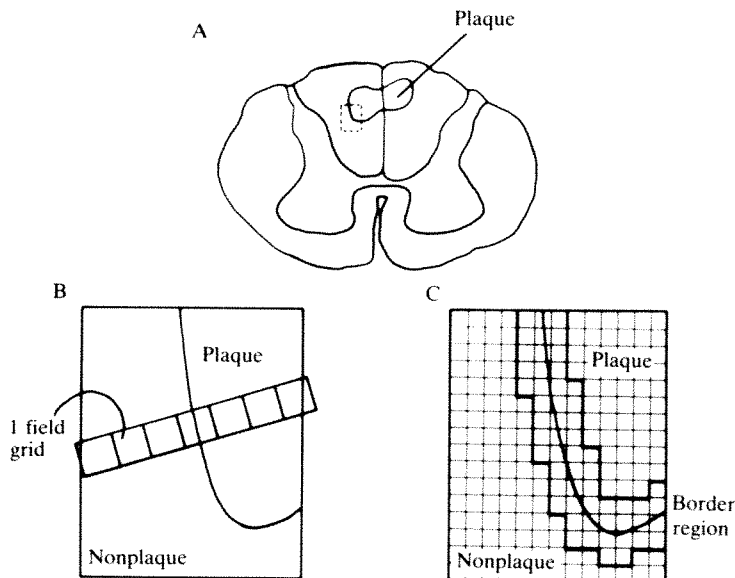


FIG. 1. Techniques for the quantitative evaluation of plaque borders. A, schematic diagram of an MS plaque in a typical CNS section. B, detail of the plaque edge: technique for the border study. One square field grid is centred on the plaque edge and 6 flanking fields were counted. This process was repeated several times along adjacent sections of the plaque edge. C, detail of the plaque edge: technique for counting 3 whole plaques. Every field in the section is counted and recorded in a plaque-shaped grid. The plaque edge is projected onto the grid and fields falling into a predefined border region are identified.

was soluble with Generalized Linear Interactive Modelling (GLIM). GLIM is a program designed to address nonorthogonal multiple regression problems (Baker and Nelder (1978)). The average number of T cells per field was low with many fields containing no immunoperoxidase stained cells. Thus a Poisson distribution was assumed and corrections were made for deviations.

#### *Quantification of plaque and nonplaque regions using a sampling technique*

Seventeen sections from 10 cases were suitable for quantification; 30 high power fields ( $\times 400$ ) were counted in the same relative white matter location in each of the sections stained with the various antibodies. Plaque and nonplaque areas were enumerated separately. The sites chosen for counting plaques included the centre, intermediate zone, and demyelinated portion of the margin. Nonplaque areas varied in location but avoided overlapping the plaque margin. Cuffs of perivascular infiltrate previously counted (Booss *et al.*, 1983) were excluded. The same locations for any given section were standardized for each of the monoclonal antibodies. Differences between the number of cells bearing OKT8, LEU3A and OKT3 markers were examined with a test for dependent paired data.

#### *Histopathological estimation of activity*

Histopathological activity was scored on the basis of three criteria: the presence of macrophages, degree of cellularity, and the presence of oil red O phagocytosed material. Eight border regions were inactive (score = 1), 4 showed some signs of activity (score = 2), and 3 were considered to be active (score = 3) in the border study.

In the study employing sampling of plaque and nonplaque regions it was not possible to score activity as precisely because the sampled regions were not uniform with respect to histopathological activity; therefore, only the predominance of activity or inactivity was considered. Six sections were considered active and 11 inactive.

#### *Counting of whole sections*

Three plaques from 3 different cases were selected in which the staining and the tissue presentation of comparable sections stained with the OKT8, LEU3A, and OKT3 T cell markers were uniform throughout the sections. The number of positive cells were tabulated for every field in the sections. This resulted in 3 data maps for each section composed of squares of equal size recording the number of positive cells found in each field. The border lines of the plaques were drawn by projection. Fields that were transected by a plaque edge as well as the adjacent whole fields were counted as 'border area'. The remaining fields were counted as plaque or nonplaque areas (fig. 1A, C). All fields in each area were added together and the mean numbers of positive cells per field were calculated.

## RESULTS

#### *T cell subsets on the border*

Scanning the sections under low power, it was noted that the number of immunoperoxidase positive cells varied greatly among the sections. While many sections had only a few positive cells, 1 had up to 25 positive cells in a high power field grid. Lymphocytes and macrophages were abundant in perivascular and vessel-associated areas in many sections. In some plaques there appeared to be a gradient of cells from the vessel decreasing outward and leading towards the border. Within each section, cells were clustered on the border. Computer estimates for the mean number of T cells of both subsets in each distance field were derived using the GLIM program and are shown in fig. 2. These estimates include both active and

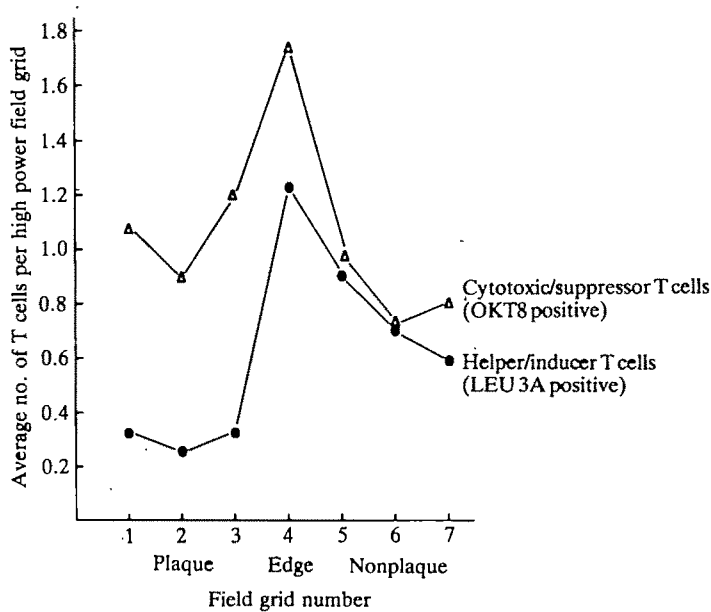


FIG. 2. Distribution of subsets across plaque edge. The vertical axis represents the number of cells per high power field grid estimated at each distance field using linear regression (GLIM). LEU3A cells are not distributed randomly across plaque borders ( $P < 0.001$ ), nor are OKT8 cells distributed randomly across plaque borders ( $P < 0.001$ ). OKT8 positive cells and LEU3A positive cells are more numerous in fields centred on the exact edge than in the flanking border fields ( $P < 0.05$  for C-S;  $P < 0.025$  for LEU3A).

inactive plaques. Although some plaques had many positive cells, the average was less than 2 cells per high power field. Both subsets peaked on the exact border and the number of cells fell off to lower values on either side. LEU3A cells immediately inside the plaque edge fell off more quickly than in the parenchyma immediately outside of the plaque edge. There was a highly significant difference in the number of cells among distance fields across the border ( $P < 0.001$  for both OKT8 and LEU3A). On the whole, the cytotoxic suppressor cells predominated. The C-S:H-I ratio was greatest in flanking fields within the plaque.

There tended to be more cells in the border fields of active plaques. We had too few histopathologically active plaques, however, to determine reliably the effect of this factor in the border area studies. Further, activity was confounded with the variability in the number of cells in sections between individuals. One of the most active plaques had many more H-I than C-S cells as well as more positively staining cells overall. This, however, was the only plaque in the border study in which the H-I subset predominated.

#### *Analysis of representative plaque and nonplaque areas*

T cells bearing the C-S differentiation antigen were found to be three times as numerous as those bearing the H-I antigen (Table 1). The differences were examined with a test for dependent paired data and found to be significant at  $P < 0.015$ . Furthermore, the C-S subpopulation was more numerous than that bearing the

TABLE 1. T CELL SUBSETS AND RATIOS IN CNS SECTIONS: A COMPARISON OF PLAQUE AND NONPLAQUE AREAS\*

|        | <i>Area sampled</i> |                  |
|--------|---------------------|------------------|
|        | <i>Plaque</i>       | <i>Nonplaque</i> |
| Pan T  | 1.12 ± 1.78         | 0.51 ± 0.50      |
| H-I    | 0.70 ± 0.54         | 0.46 ± 0.47      |
| C-S    | 2.14 ± 2.32         | 1.34 ± 1.32      |
| HI/C-S | 0.33                | 0.35             |

\*T cell subsets and ratios in plaque and nonplaque areas of 17 CNS sections from 11 cases of MS. Data are recorded as the number of antigen positive cells ± SD per high power field (× 400); 30 high power fields were counted for each region. Statistical analysis is given in the text.

pan-T cell marker. The same level of significance was achieved for this comparison. Under the same conditions in other tissues (spleen, tonsil, and lymph node) we found an appropriate equivalence between the sum of the subsets and the number of cells bearing the pan-T cell marker.

Active and inactive plaques were compared with respect to T cell populations in plaque and normal appearing nonplaque regions. As shown in Table 2, the number

TABLE 2. T CELL SUBSETS AND RATIOS IN CNS SECTIONS: A COMPARISON OF ACTIVE AND INACTIVE PLAQUES\*

|         | <i>Active</i><br>6 cases, 6 sections |                  | <i>Inactive</i><br>5 cases, 11 sections |                  |
|---------|--------------------------------------|------------------|-----------------------------------------|------------------|
|         | <i>Plaque</i>                        | <i>Nonplaque</i> | <i>Plaque</i>                           | <i>Nonplaque</i> |
| Pan-T   | 1.79 ± 2.45                          | 0.35 ± 0.20      | 0.75 ± 1.28                             | 0.59 ± 0.60      |
| H-I     | 0.81 ± 0.49                          | 0.41 ± 0.55      | 0.65 ± 0.59                             | 0.49 ± 0.45      |
| C-S     | 2.33 ± 2.69                          | 0.64 ± 0.53      | 2.04 ± 2.22                             | 1.72 ± 1.48      |
| H-I/C-S | 0.35                                 | 0.64             | 0.32                                    | 0.28             |

\*T cells in active and inactive plaques are compared. Data are recorded as the number of antigen positive cells ± SD per high power field (× 400); 30 high power fields were counted for each region. Statistical analysis is given in the text.

of H-I cells was very similar in active or inactive plaques and in nonplaque areas, whether adjacent to active or inactive plaques. The number of C-S cells in plaque areas was also not obviously related to the plaque activity. However, in nonplaque areas associated with active plaques there were considerably fewer C-S cells than in nonplaque areas associated with inactive plaques. When these data were compared with an independent random sample test for unequal variances, the difference was found to be significant at  $P < 0.05$ .

### *Counts of complete sections*

All previous studies of T cell subsets in MS lesions have used qualitative methods or used sampling techniques for quantification. In addition to the vector method of sampling the border, we have determined the absolute distribution of T cell subsets in 3 whole sections.

Fig. 3 compares the number of C-S cells to the number of H-I cells per high



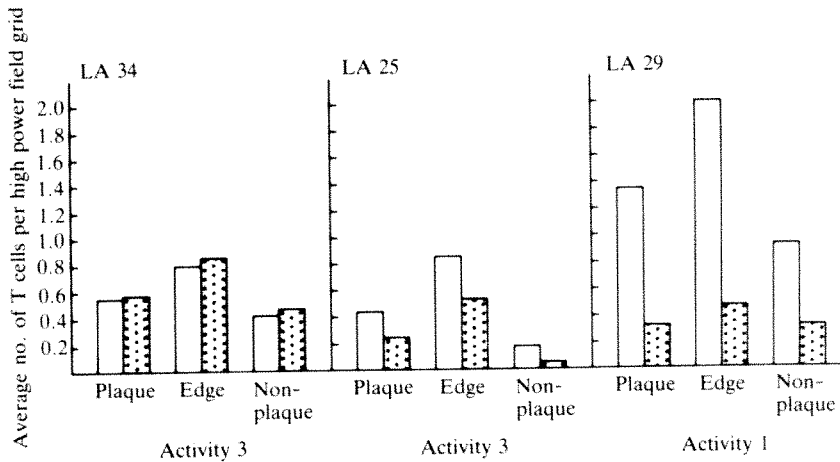


FIG. 3. Comparison of T cell subsets in 3 whole plaques. Dotted columns = H-I or LEU3A; open columns = C-S or OKT8. Activity 3 = active; activity 1 = inactive.

power field grid of 3 fully counted plaques. Sections LA 34 and LA 25 are active and section LA 29 is inactive. The plaque edge includes the approximate equivalent of the border field and 2 flanking fields (compare with fig. 1A, C). The average number of C-S cells per high power field was greater in the plaque than in the nonplaque areas in all 3 sections. This area also showed a relative clustering of T cell subsets. LA 29, the inactive plaque, had the greatest number of C-S cells and the greatest ratio of C-S to H-I cells in all 3 regions. Furthermore, the numbers of C-S and H-I T cells in LA 34, an active plaque, were nearly equal.

The average number of pan-T cells was found to be less than the number of C-S cells in samples of plaque and nonplaque regions (Table 1). We therefore counted the pan-T cells as well as the T cells subsets in the 3 whole sections with particular interest in any association of this discrepancy with the plaque border. Fig. 4 compares the sum of the C-S and H-I T cells to the number of cells bearing the pan-T cell marker in plaque, nonplaque, and in border areas. The sum of the subsets is greater than the number of pan-T cells in 2 plaque and in 2 edge regions. Section LA 34 containing the most active plaque edge, has significant discrepancies in 2 regions. This section has the greatest number of H-I cells with a few more H-I cells than C-S cells in each of the 3 regions.

## DISCUSSION

The region of greatest increase in cellularity in MS has been the edge of the lesion. The plaque edge, the interface between plaque and normal myelin, is the immunological environment in which plaque expansion occurs. Investigators have previously studied lymphocytes associated with MS plaques. Plasma cells have been demonstrated to be associated with active plaques (Esiri, 1980). In addition, areas of lymphocytic cuffing associated with small vessels in and around plaques

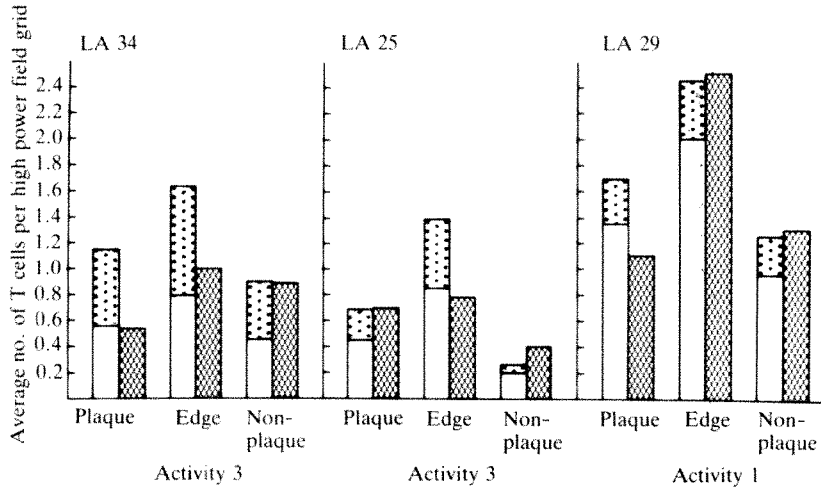


FIG. 4. Comparison of the sum of the subsets to the number of pan-T cells in 3 whole plaques. OKT8 + LEU3A > T3 in 2 border regions and in 2 plaque regions. Dotted columns = H-I; open columns = C-S; cross-hatched columns = Pan T cell (OKT3). Activity 3 = active; activity 1 = inactive.

have been shown to contain many T lymphocytes (Booss *et al.*, 1983; Hauser *et al.*, 1986). Traugott *et al.* (1983) found H-I and C-S cells increased in numbers from the centre to the edge of active chronic lesions and H-I cells penetrated into the normal parenchyma. Three studies (Booss *et al.*, 1983; Hauser *et al.*, 1986; Woodroffe *et al.*, 1986) noted an overrepresentation of C-S cells compared to H-I cells in the cellular infiltration of the parenchyma as well as in regions of perivascular cuffing. In the study of Hauser *et al.* (1986), biopsy and autopsy specimens gave similar results, thereby controlling for potential autolytic changes. One of the objectives of the present studies was to evaluate the distribution of T cell subsets about the plaque border.

We have found that both the C-S and the H-I subsets peaked on the exact border. However, the C-S and H-I distribution curves formed different patterns across the border. At distances further from the edge fewer cells of either subset are present. With the exception of fields centring on vessels that exhibit lymphocytic cuffing, no fields have more cells of either subset than those associated with the exact edge of demyelination. The apparent local difference in the immune balance associated with the border of demyelination is difficult to interpret. It describes a nonuniform relationship between subsets and invokes the notion of opposing active roles for the two types of cells rather than one of a uniform effector response.

The average number of T cells per plaque is small and varies greatly. In the CNS of patients with no known CNS disease, the average number of LEU3A cells was 0.13 while the average number of OKT8 cells was 0.26 in each field (Booss *et al.*, 1983). The number of C-S and H-I cells on the exact border of all MS plaques (inactive and active) that were studied was in the range of 1 to 2 cells (i.e., a ten fold increase over control levels). Many factors might effect the number of T cells including plaque activity, present or past therapies, and the proximity of the plaque

to vessels. It is not clear whether plaque evolution involves only a few T cells or whether large numbers of T cells are present for a brief period of time not adequately described by these data. If active demyelination is achieved by other cells or factors, the small absolute number of T cells reflect a regulatory rather than an effector role for these lymphocytes.

It is possible that a change in the ratio of T cell subsets is correlated with a change in plaque activity. In our studies, plaque sampling revealed that the number of H-I cells was very similar in white matter surrounding both active and inactive plaques. However, in the nonplaque areas associated with active plaques there were fewer C-S cells than in nonplaque areas associated with inactive plaques. The increased number of C-S cells in nonplaque white matter associated with inactive plaques was significant at  $P < 0.01$ . The border study sampled the 7 border fields in a set of predominantly inactive plaques and revealed a C-S dominance at the border. H-I cells outnumbered the C-S cells in 1 active plaque. Several other active plaques had nearly equal numbers of the two subsets including the 2 active plaques in the whole plaque study. These findings, when taken together with the statistically significant sampling study, lead to a tempting thesis that lesion progression in MS is associated with the local predominance of H-I T cells while stabilization is associated with the local predominance of C-S T cells.

This thesis is strengthened by similar observations in experimental allergic encephalomyelitis (EAE). CNS infiltration by macrophages and T cells (Hickey *et al.*, 1983; Sobel *et al.*, 1984) in early lesions is associated with predominantly Lyt-1 (H-I) lymphocytes (Hauser *et al.*, 1984a). It was shown that mice depleted of their T cells could be immunized to develop EAE regularly only after reconstitution with cells bearing the H-I (Lyt-1) marker (Hauser *et al.*, 1984b). Brostoff and Mason (1984) demonstrated that monoclonal antibody directed against rat helper T cells reduced the duration of symptoms in rats treated after the appearance of clinical signs. Further, Hickey and Gonatas (1984) showed a persistence of OX8 cells (C-S) associated with the symptom-free stage.

The previous finding that C-S cells outnumber pan-T cells in sampled plaque and nonplaque regions (Booss *et al.*, 1983) was unexpected. We attempted to eliminate the possibility that the predominance was due to errors in technique by the use of controls. Under the same experimental conditions in other tissues we found an approximate equivalence between the sum of the subsets and the number of cells bearing the pan-T cell marker. In our preliminary studies, use of the pan-T cell antibody T-28 (UCHT1 had also demonstrated that C-S T cells outnumbered pan-T cells. Woodroffe *et al.* (1986) have used T-28 and also found that the combined subsets appeared to exceed the number of pan-T cells in many perivascular cuffs. In our own studies, quantification with a different antibody, T11A (against the sheep red blood cell receptor), did not alter the discrepancy. Oligodendrocytes did not stain with C-S antibody in control tissues to account for the apparent excess of C-S cells compared to the pan-T cells. In the present study of 3 whole plaques, subsets summed to equal pan-T cells in some areas, suggesting

that the discrepancy was nonuniform. Interestingly, in this small sample, only plaque and border areas had fewer than expected cells bearing the pan-T cell marker. This preliminary finding suggests that the expression of the pan-T cell marker may be affected by the disease process. A similar discrepancy between pan-T cell and subset-T cell markers in the CNS has been observed in a study of gliomas (von Hanwehr *et al.*, 1984).

It is tempting to attribute the observation that the C-S cells are more numerous than the cells bearing the pan-T marker to antigenic modulation. It is reasonable to postulate a decrease in the expression of the pan-T cell marker in certain cytotoxic-suppressor cells. Antibodies against T cells have been found in certain autoimmune diseases (Morimoto *et al.*, 1981, 1984). It has been shown that T3 modulation by anti-T3 antibody has no effect on T cell viability but decreases cytotoxic effector function of T4 and T8 clones for up to 48 h. In addition, the proliferative response to IL2 was greater in these cells (Acuto and Reinherz, 1985). It appears that altered antigen recognition and disturbed T cell function are associated with T3 modulation. If modulation is present in MS, its role in pathogenesis is intriguing.

A potential mechanism to be considered is biochemical modification of the surface markers of lymphocytes. It is known, for example, that MS tissue has a greater content of lysosomal enzymes than does control tissue (Allen and McKeown, 1979). The finding of Hauser *et al.* (1986) that biopsy and autopsy samples were similar, while controlling for postmortem autolysis, does not exclude the possibility that biochemical modification of surface markers might occur in life. Such modification could have a significant functional effect.

Another paradigm, the presence of a T8 bearing non-T cell population, might explain the presence of OKT8 positive, OKT3 negative cells. There is precedent in hepatitis B which has several correlates with MS both in the active-chronic nature of the disease and in the patterns of tissue infiltration by inflammatory cells. Colucci *et al.* (1983) reported that the sum of the subsets outnumbered the pan-T cells in 5 out of 26 cases of chronic active hepatitis. In acute hepatitis, Eggink *et al.* (1984) found LEU7+ (NK cells) and OKT8+, OKT1-, OKT3- cells predominated over OKT8+, OKT1+, OKT3+ cells. In contrast, chronic hepatitis B sections had a predominance of OKT8+, OKT1+, OKT3+ cells (Eggink *et al.*, 1982). Clearly, further studies are required to determine if the cells bearing OKT8 but not OKT3 antigen in MS are NK cells.

A major goal in the investigation of T cells in MS is to uncover patterns which suggest rational therapeutic intervention. Immunotherapy might focus on the H-1/C-S balance. However, the functional significance of the C-S dominance in the CNS must be clarified. If C-S cells have a suppressor function, immunotherapy ought to be tailored to increase suppression or decrease help. If these cells are instead primarily cytotoxic, we ought to decrease cytotoxic activity. Studies of the specific functional roles of immune cell subsets in the parenchyma of the CNS are clearly needed.

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## CHOLINESTERASE ACTIVITIES IN CEREBROSPINAL FLUID OF PATIENTS WITH SENILE DEMENTIA OF ALZHEIMER TYPE

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### SUMMARY

Acetylcholinesterase (AChE) and nonspecific cholinesterase (nsChE) activities of lumbar cerebrospinal fluid (CSF) from patients with a clinical or histological diagnosis of Alzheimer's disease have been compared with those of normal age-matched control patients and patients with dementia of non-Alzheimer aetiology. No significant differences in the AChE activity of lumbar CSF from histologically and clinically diagnosed Alzheimer's disease patients and normal age-matched controls were found, although they could be distinguished from controls and other dementias by their lower lumbar CSF levels of nsChE activity and by their elevated ratio of AChE/nsChE. A lower level of AChE activity was observed in the lumbar CSF of patients with dementia of non-Alzheimer aetiology.

The AChE and nsChE activities of ventricular CSF obtained at postmortem have also been examined. The AChE activity of the ventricular CSF of patients with histologically confirmed Alzheimer's disease was 66% lower than that of age-matched controls; these patients could also be distinguished from normals by their lower levels of nsChE and by the elevated ratio of AChE/nsChE activities. A molecular defect in the AChE in the ventricular CSF of Alzheimer patients is indicated by the finding that the enzyme failed to show inhibition by high concentrations of substrate.

The lower level of AChE in ventricular CSF may reflect the changes in this enzyme in forebrain regions of Alzheimer patients. Although it is at present not possible to correlate the lower levels of nsChE found in CSF with any known brain pathology, the significantly altered ratio of AChE/nsChE activities in lumbar CSF may possibly form the basis for a diagnostic test of Alzheimer type dementia.

### INTRODUCTION

Biochemical and histochemical studies have demonstrated a widespread deficit in the activity of acetylcholinesterase (AChE) in the brains of patients with senile dementia of the Alzheimer type (SDAT) at postmortem (*see Hardy et al.*, 1985, for review). The extent of these reductions in AChE activity was found to be correlated with the severity of the dementia at death, that is, with the number of

neuropathological abnormalities and with the mental test score of the patients (Perry *et al.*, 1978). It has been noted that all the cell groups outside the cortex in which the typical pathological abnormalities, such as cell loss and/or plaques and tangles are found in Alzheimer's disease, contain AChE (Smith and Cuello, 1984), and these authors have suggested that the disease is connected with an abnormality of some of the cells that contain AChE. Consistent with such an idea is the finding that cortical AChE from patients with SDAT exhibits abnormal kinetic properties and is no longer subject to substrate inhibition, unlike that from normal age-matched controls (Perry and Perry, 1981). The plaques which are a feature of the disease have been shown to stain positively for AChE (Perry *et al.*, 1980; Perry and Perry, 1981), indicating that the neurites and terminals forming the plaque (Probst *et al.*, 1983) may be derived from AChE-containing cells. Indeed, AChE-staining neurite-like structures have been identified in the plaques of elderly monkeys (Struble *et al.*, 1982).

One soluble isoenzyme of AChE is secreted from certain brain regions of animals on electrical and drug stimulation (Greenfield, 1984) and AChE is present in human cerebrospinal fluid (CSF) (Tower and McEachern, 1949). It might therefore be predicted that low levels of brain tissue AChE would be reflected in lower levels of AChE in the CSF. However, studies of AChE activity in lumbar CSF from patients with dementia have produced conflicting results; several authors report a significant decrease in the AChE activity of patients with SDAT (Soininen *et al.*, 1981; Arendt *et al.*, 1984; Tune *et al.*, 1985), whereas other authors (Davies, 1979; Wood *et al.*, 1982; Deutsch *et al.*, 1983; Lal *et al.*, 1984) report no change, or a slight tendency for an increase (Johnson and Domino, 1971) in levels of the enzyme in lumbar CSF. A wide variety of assay conditions and techniques have been employed in these studies, with only one of them (Arendt *et al.*, 1984) using the specific AChE inhibitor BW284c51 to distinguish between 'true' acetylcholinesterase and nonspecific cholinesterase in all their samples. Thus most studies actually report total cholinesterase activity, rather than AChE activity, as they claim. The main criticism of the above studies is that (with the exception of the study by Arendt *et al.*, 1984) diagnosis of Alzheimer's disease was based mainly on clinical criteria, and rarely confirmed by postmortem or histological examination. A definite diagnosis of Alzheimer's disease is only possible if the neuropathology of the disease is demonstrated in samples of brain material, that is the presence of senile plaques and neurofibrillary tangles. In the present work, the 'true' AChE activities of lumbar CSF from patients who have had the clinical diagnosis of Alzheimer's disease confirmed by cortical biopsy have been examined and compared with those of age-matched controls. The results, which are reported in this paper, have been compared with those from a study of lumbar CSF AChE activity in patients with a purely clinical diagnosis of Alzheimer's disease using strict criteria. The AChE activity of ventricular CSF obtained at postmortem has also been examined in patients with a histological diagnosis of Alzheimer's disease. A brief report of some of the results from the latter study has been published (Appleyard *et al.*, 1983). In



all cases, patients with dementia of non-Alzheimer aetiology and nondemented controls were also studied.

In view of the reported alterations in the kinetic properties of AChE in cortical homogenates from patients with SDAT (Perry and Perry, 1981), the CSF samples have been examined to see if AChE is inhibited by high substrate concentrations in patients with the disease.

The activities of AChE and butyrylcholinesterase (BuChE) are altered in opposite directions in the brain (Perry *et al.*, 1978) and plasma (Smith *et al.*, 1982) of patients with Alzheimer's disease, and this might be reflected in a decrease in the ratio of AChE/BuChE in the CSF of patients with the disease. Indeed, Arendt *et al.* (1984) found such a decrease in their series of histologically-diagnosed patients. The AChE/BuChE ratios have therefore been examined in the three series of patients reported in this paper.

## METHODS

### *Patients*

*1. Clinical diagnosis only.* Eleven patients with senile dementia of the Alzheimer type (SDAT), 8 patients with dementia of uncertain aetiology and 15 controls with no evidence of dementia or other neurological disease were studied. All patients were assessed prospectively and diagnosed on the basis of their performance on an abbreviated Mental Test Score (Hodkinson, 1972) and the modified Kew Test (McDonald, 1969; Hare, 1978) and by an activity of daily living assessment. For all SDAT patients all other possible causes of dementia were excluded by laboratory tests, the Hachinski Score (Hachinski *et al.*, 1975) and in 6 patients by CT scan. Patients in the 'mixed' group included 4 patients with clinical evidence of multi-infarct dementia and 3 patients with a history of progressive dementia that could be attributed to other factors (recent Herpes zoster, prolonged haemodialysis for membranous glomerulonephritis or serological evidence of treponemal disease). A further patient was shown to have a depressive illness with memory disturbance improving markedly, although not to normal, with antidepressant treatment (pseudodementia). All patients in the control group complained of low back pain with or without sciatica, and were attending for myelography. In all patients myelography was either normal or revealed evidence of a disc lesion without evidence of a spinal block. None had a history of memory disturbance.

Two SDAT patients were receiving tricyclic antidepressants and 1 a phenothiazine while in the mixed group one was receiving L-DOPA and anticholinergic drugs, 1 was receiving carbamazepine and another prednisolone. Control patients were not receiving psychoactive drugs other than mild hypnotics.

CSF was obtained after 1–2 h of recumbency using a standard lumbar puncture technique, and sent for microbiological, serological and biochemical analysis as clinically indicated. After discussion with relatives, where necessary, informed consent for the removal of an additional 1–2 ml for acetylcholinesterase estimation was obtained for all individuals. Samples were kept at 4° C until centrifugation, and stored at –70° C until analysis. All samples were clear and free of blood.

*2. Clinical diagnosis with histological confirmation at brain biopsy.* Seven patients with senile dementia of the Alzheimer type, 4 patients with dementia of uncertain aetiology, and 6 controls with no evidence of dementia or other neurological diseases were studied. The procedure of cerebral biopsy was approved by the Manchester Central District Ethical Committee.

All patients were assessed for cognitive impairment shortly before surgery (*see* Neary *et al.*, 1986). Patients in the SDAT group all had a clinical diagnosis of Alzheimer's disease and showed the characteristic histopathological abnormalities (plaques and tangles) in neocortical tissue removed at

diagnostic craniotomy. Patients in the non-SDAT group had a clinical diagnosis of probable SDAT but did not display the histological changes that are characteristic of the disease upon examination of neocortical biopsy samples. Patients in the control group were all undergoing investigation for a variety of peripheral and spinal complaints.

CSF (0.5–5.0 ml) was removed before operation from the lumbar subarachnoid space, following overnight fast, and frozen at  $-70^{\circ}\text{C}$  until analysis. All patients were drug free at the time of the lumbar puncture.

3. *Postmortem diagnosis of Alzheimer's disease.* Ventricular CSF obtained at postmortem on separate groups of demented and intellectually unimpaired elderly subjects was studied. All patients were assessed prospectively during life using the same techniques described in Section 1. Blood-free samples were stored at  $-70^{\circ}\text{C}$  until analysis and centrifuged prior to assay.

The ages (range 67–100 yrs), postmortem delay (range 0–4 days) and storage time before assay were similar for all groups of patients. The medication of the Alzheimer's disease and control patients was similar with the most frequently prescribed drugs being phenothiazines, butyrophenones and tricyclic antidepressants.

#### *Biochemical analysis*

All biochemical analyses were performed without prior knowledge of the diagnosis.

Acetylcholinesterase activity was measured at  $V_{\max}$  by a modified version (Chubb and Smith, 1975) of the method of Ellman *et al.* (1961). Acetylthiocholine (1.0 mM) was used as substrate and the assay was performed in 0.05 M Na/K phosphate buffer, pH 7.0 at  $30^{\circ}\text{C}$ . In order to distinguish between AChE and nonspecific cholinesterase activity assays were performed both in the presence and absence of the specific AChE inhibitor BW284c51 ( $1.5 \times 10^{-5}\text{ M}$ ).

The assay conditions described above allow an estimation of the nonspecific cholinesterase activity present in the samples, but do not provide an accurate quantitative measure of butyrylcholinesterase activity, since the substrate concentration used is suboptimal for this enzyme. BuChE activity was also measured by the modified version of the Ellman method using  $1.5 \times 10^{-2}\text{ M}$  butyrylthiocholine as substrate, which is optimum for this enzyme but is not a substrate for AChE.

Estimation of the protein content of the CSF was performed by the method of Lowry *et al.* (1951), following precipitation by 6% trichloroacetic acid.

All samples of a sufficient volume were assayed for AChE activity at various substrate concentrations from 0.1 to 20 mM acetylthiocholine to determine whether the enzyme showed substrate inhibition. Only a limited volume of ventricular CSF was available for study. In this case 19 control samples and 9 samples of CSF from patients with SDAT were analysed to determine whether the AChE was subject to substrate inhibition by comparing the activities of the samples at substrate concentrations of 1 mM and 20 mM acetylthiocholine. These substrate concentrations were chosen after examination of the complete substrate curves obtained for 6 control samples; peak AChE activity occurred at substrate concentrations of 1 to 2 mM acetylthiocholine whilst marked inhibition of activity was observed at 20 mM acetylthiocholine.

#### *Statistical analysis*

Data are presented as the mean  $\pm$  SEM. Results were analysed by Student's *t* test and by the Spearman rank correlation test.

## RESULTS

### *Lumbar CSF from patients with a purely clinical diagnosis*

The mean AChE activity of lumbar CSF, expressed both per ml CSF and per mg protein, from patients with clinical dementia of non-Alzheimer aetiology was

markedly lower than in age-matched controls, whereas control levels were observed in patients with SDAT (Table 1, fig. 1).

The mean nsChE activity (measured with a substrate of 1.0 mM acetylthiocholine) in CSF from patients with SDAT was significantly lower than in controls (Table 1, fig. 1). However, when the Alzheimer's patients were subclassified according to the severity of the dementia, as determined by their performance on the Kew Test, there was no difference in the nsChE activity from patients with severe dementia compared with that in patients with mild dementia. The patients with dementia of non-Alzheimer aetiology had nsChE activities in their CSF that were not significantly different from those observed in normal aged subjects (Table 1).

TABLE 1. CHOLINESTERASE ACTIVITIES AND PROTEIN CONTENT OF LUMBAR CSF FROM PATIENTS WITH A CLINICAL DIAGNOSIS OF DEMENTIA<sup>1</sup>

| Disease                    | Ages<br>(yrs) | AChE      | nsChE     | Protein<br>(g/l) | SA AChE   | AChE/BuChE  |
|----------------------------|---------------|-----------|-----------|------------------|-----------|-------------|
| Control (<50 yrs, n=4)     | 37.0±1.7      | 13.5±1.8  | 3.2 ±0.4* | 0.33±0.05        | 43.8±9.5  | 1.79±0.21** |
| Control (>50 yrs n=12)     | 59.5±2.1      | 19.2±2.3  | 5.2 ±0.6  | 0.42±0.06        | 43.8±9.5  | 0.88±0.10   |
| SDAT (n=11)                | 68.9±2.0      | 16.9±1.3  | 3.42±0.5* | 0.33±0.03        | 55.2±9.9  | 1.34±0.15*  |
| Non-SDAT dementia<br>(n=6) | 76.0±3.9      | 10.4±1.6* | 6.8 ±3.5  | 0.57±0.26        | 28.1±6.1* | 0.82±0.13   |
| Pseudodementia (n=1)       | 77.0          | 15.4      | 1.94      | 0.225            | 68.4      | 2.56        |

<sup>1</sup>Acetylcholinesterase (AChE), nonspecific cholinesterase (nsChE) activities are expressed as nmol acetylthiocholine hydrolyzed/min/ml CSF; butyrylcholinesterase (BuChE) activity is expressed as nmol butyrylthiocholine hydrolysed/min/ml CSF. Specific activity (SA) AChE is expressed per mg protein. \*, \*\* Significantly different from controls (>50 yrs) with  $P<0.05$  and  $P<0.005$ , respectively.

A similar situation was also observed with BuChE activity (measured with  $1.5 \times 10^{-2}$  M butyrylthiocholine as substrate). BuChE activity of CSF from cases with SDAT ranged from 3.82 to 26.3 mU/ml, and the mean value (13.6) was significantly ( $P<0.025$ ) lower (by 35%) than that for controls (mean, 20.8; range 11.3 to 35.4 mU/ml).

The ratio of AChE activity to BuChE activity or to nsChE activity in the patients with SDAT was significantly elevated over the ratio observed in control (>50 yrs old) patients; this ratio was unchanged in patients with dementia of non-Alzheimer aetiology (Table 1, fig. 1).

Age-related changes in AChE, nsChE and ratio AChE/BuChE were also observed.

#### *Lumbar CSF from patients with a biopsy-confirmed diagnosis*

The results obtained in this group of patients were similar to those observed in the patients with a purely clinical diagnosis. The AChE activity of CSF, expressed per ml CSF and per mg protein, from patients with dementia of non-Alzheimer aetiology tended to be lower than those in the CSF from age-matched controls; in

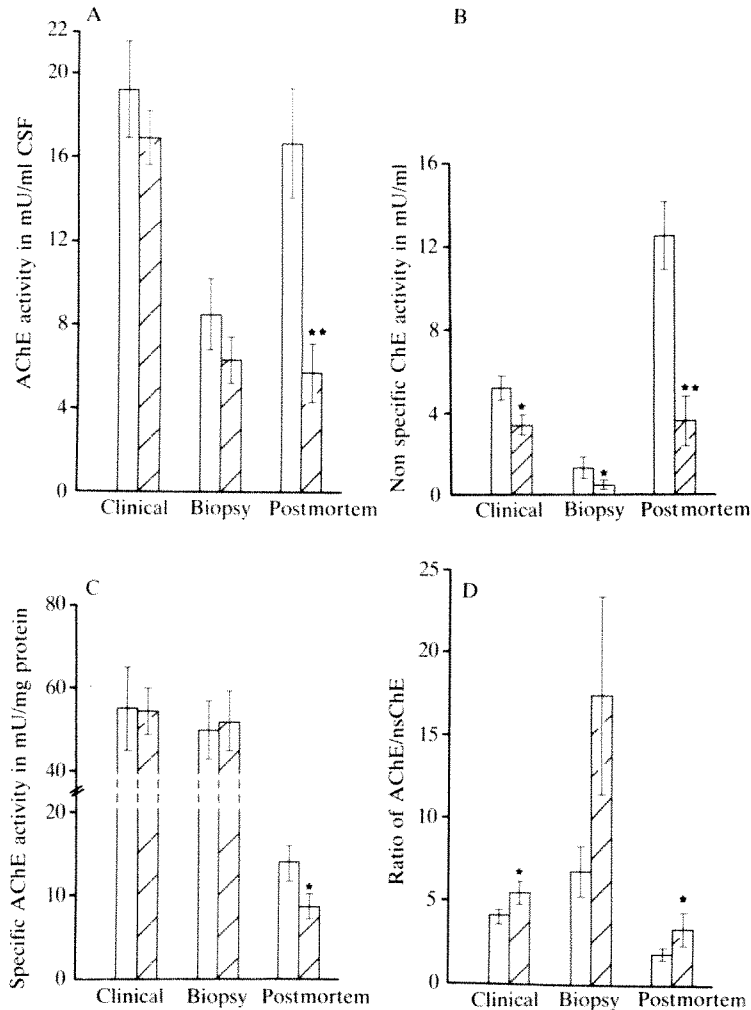


FIG. 1. Cholinesterase activities in lumbar and ventricular CSF from patients with a diagnosis of Alzheimer's disease. Clinical group = patients with a purely clinical diagnosis of Alzheimer's disease; biopsy group = clinical diagnosis confirmed by histological examination at biopsy; in both groups lumbar CSF was examined. Postmortem group = ventricular CSF obtained at postmortem from patients with a histological diagnosis of Alzheimer's disease. Open columns = normal age-matched control patients with no evidence of neurological disease; cross-hatched columns = Alzheimer's disease patients. Acetylcholinesterase (A) and nonspecific cholinesterase (B) activities are expressed as nmol acetylthiocholine hydrolyzed/min/ml CSF. Specific activity acetylcholinesterase (C) is expressed as nmol acetylthiocholine hydrolysed/min/mg protein. \*, \*\* Significantly different from control with  $P < 0.05$  and  $P < 0.005$ , respectively.

those with SDAT the levels were normal (Table 2, fig. 1). Nonspecific cholinesterase activity (measured with a substrate of 1.0 mM acetylthiocholine) was markedly lower than controls in the patients with SDAT, but unchanged in the patients with dementia of non-Alzheimer aetiology (Table 2).

The ratio of AChE activity to BuChE activity or to nsChE activity in the patients with SDAT tended to be higher than that observed in normal control patients (Table 2, fig. 1), and there was a significant correlation between this ratio and the

<sup>1</sup> Acetylcholinesterase (AChE) and nonspecific cholinesterase (nsChE) activities are expressed as nmol acetylthiocholine hydrolysed/min/ml CSF; specific activity acetylcholinesterase is expressed per mg protein; protein content is expressed as mg/ml CSF. \* Significantly different from controls with  $P < 0.05$ . † Significantly different from controls with  $P < 0.05$  by the Wilcoxon test.

TABLE 2. CHOLINESTERASE ACTIVITIES AND PROTEIN CONTENT OF LUMBAR CSF FROM PATIENTS WITH A HISTOLOGICAL DIAGNOSIS (FROM CORTICAL BIOPSY) OF ALZHEIMER'S DISEASE<sup>1</sup>

| Diagnosis                 | AChE         | nsChE        | Protein     | SA AChE    | AChE/ChE    |
|---------------------------|--------------|--------------|-------------|------------|-------------|
| Controls (n = 6)          | 8.44 ± 1.75  | 1.32 ± 0.48  | 0.18 ± 0.03 | 50.3 ± 7.1 | 6.81 ± 1.42 |
| SDAT (n = 7)              | 6.32 ± 1.11  | 0.48 ± 0.18* | 0.12 ± 0.02 | 52.1 ± 7.2 | 17.3 ± 7.7  |
| Non-SDAT dementia (n = 4) | 4.43 ± 0.66† | 0.91 ± 0.20  | 0.17 ± 0.03 | 28.9 ± 5.8 | 5.45 ± 1.09 |

cognitive impairment rating of the SDAT patients with a correlation coefficient of 0.7590. The ratio in patients with non-SDAT dementia however, was not different from that in control patients (Table 2).

#### *Ventricular CSF obtained at postmortem*

The mean AChE activity in ventricular CSF obtained at autopsy from SDAT patients was markedly lower than in controls (Table 3, fig. 1). Two patients were diagnosed clinically as having mild Alzheimer's disease and showed normal cortical ChAT levels at postmortem examination. The AChE activities of the CSF from these patients were in the normal range (13.4 and 14.7 mU/ml). However, there was no correlation between the AChE activities of the CSF samples from SDAT cases with the severity of the dementia as determined by cortical plaque and tangle counts. The AChE activities of ventricular CSF from patients with other neurological diseases, including non-Alzheimer dementia, Parkinson's disease and depression, were not significantly different from control levels (*see* Table 1).

The mean nsChE activity in CSF from patients with Alzheimer's disease was also lower than in controls (Table 3, fig. 1) and again the nsChE activities of the CSF from the 2 patients with mild SDAT were in the normal range (2.36 and 9.73 mU/ml). The nsChE activities of ventricular CSF from patients with Parkinson's disease, non-Alzheimer dementia or depression were not significantly different from control levels (*see* Table 3), although the nsChE activity from patients who had recently suffered from cerebrovascular lesions (strokes) was elevated over control levels. BuChE activities were not measured due to lack of sample.

In the ventricular CSF samples from patients with SDAT there was a significant correlation ( $P < 0.02$ ) between AChE and nsChE activities ( $r = 0.723$ ). The ratio of AChE to nsChE activity in the CSF from patients with SDAT was higher than that of control patients (Table 3, fig. 1), whereas the AChE/nsChE ratios from the patients with other neurological diseases were in the control range (Table 3).

The mean TCA-precipitable protein content was significantly lower in the SDAT patients; again the values for the 2 patients with mild SDAT were in the normal range (0.98 and 1.06 mg/ml). The protein contents of CSF samples from patients

TABLE 3. CHOLINESTERASE ACTIVITIES AND PROTEIN CONTENT OF VENTRICULAR CSF OBTAINED AT POSTMORTEM FROM PATIENTS WITH DEMENTIA AND VARIOUS OTHER NEUROLOGICAL DISEASES<sup>1</sup>

| <i>Disease</i>                                | <i>Age<br/>(yrs)</i> | <i>AChE</i>   | <i>nsChE</i>  | <i>Protein<br/>(g/l)</i> | <i>SA AChE</i> | <i>AChE/ChE</i> |
|-----------------------------------------------|----------------------|---------------|---------------|--------------------------|----------------|-----------------|
| Controls<br>(n = 23)                          | 83.2 ± 1.9           | 16.7 ± 2.6    | 12.4 ± 1.6    | 1.31 ± 0.17              | 13.9 ± 2.0     | 1.78 ± 0.36     |
| SDAT (n = 11)                                 | 81.2 ± 4.7           | 5.71 ± 1.37** | 3.52 ± 1.16** | 0.66 ± 0.13*             | 8.81 ± 1.43*   | 3.42 ± 1.04*    |
| Parkinson's<br>disease (n = 6)                | 78.0 ± 3.7           | 10.9 ± 2.8    | 12.9 ± 4.9    | 1.24 ± 0.18              | 8.78 ± 1.94    | 1.08 ± 0.25     |
| PD/dementia<br>(n = 5)                        | 82.0 ± 2.5           | 18.2 ± 5.5    | 21.3 ± 8.6    | 1.63 ± 0.21              | 10.8 ± 2.06    | 1.08 ± 0.25     |
| Non-SDAT<br>dementia<br>(n = 5)               | 81.2 ± 1.4           | 21.3 ± 3.6    | 10.8 ± 0.73   | 1.35 ± 0.07              | 16.6 ± 3.91    | 1.99 ± 0.31     |
| Strokes (n = 10)                              | 81.6 ± 2.8           | 19.8 ± 5.1    | 24.4 ± 4.1 ** | 1.86 ± 0.20*             | 12.4 ± 2.9     | 1.14 ± 0.26     |
| Other neuro-<br>logical dis-<br>eases (n = 2) | 76.0                 | 24.7          | 26.5          | 3.19                     | 7.8            | 1.01            |

<sup>1</sup> Acetylcholinesterase (AChE) and nonspecific cholinesterase (nsChE) activities are expressed as nmol acetylthiocholine hydrolyzed/min/ml CSF. Specific acetylcholinesterase (SA AChE) activity is expressed per mg protein. \*, \*\* Significantly different from controls with  $P < 0.05$ ,  $P < 0.005$ , respectively. (Nine of the Alzheimer patients and 14 of the control patients are the same as those in a brief early report of this work (Appleyard *et al.*, 1983); tissue samples from these patients have been included in two previous studies (Wilcock and Esiri, 1982; Wilcock *et al.*, 1982).)

with other neurological diseases were also in the control range (*see* Table 3). Both AChE and nsChE activities significantly correlated with the protein content in the Alzheimer's cases (*fig. 2*).

#### *Substrate inhibition of AChE*

All samples of lumbar CSF obtained from patients with a clinical diagnosis exhibited profound substrate inhibition at acetylthiocholine concentrations of 20 mM, with peak activity occurring at 1 to 2 mM acetylthiocholine.

Samples of ventricular CSF obtained at postmortem were also assessed for substrate inhibition of AChE. All the control samples exhibited marked substrate inhibition at 20 mM acetylthiocholine compared to the AChE activities observed at 1 mM acetylthiocholine (ratio 20 mM/1 mM activities =  $0.346 \pm 0.054$ ), while the AChE in the CSF from patients with Alzheimer's disease failed to exhibit any such substrate inhibition with similar activities being measured at 1 mM and 20 mM acetylthiocholine (ratio 20 mM/1 mM activities =  $0.947 \pm 0.163$ ). An alternative interpretation of these results is that the substrate curve of AChE is displaced in Alzheimer's disease such that peak activity will no longer be observed at 1 mM acetylthiocholine. However, enough sample volume was available from 3 patients to allow substrate curves for AChE activity at various concentrations of acetylthiocholine from 0.1 to 20 mM to be performed. These samples failed to exhibit inhibition over this range of substrate concentrations.

## DISCUSSION

*Cholinesterases and dementia*

The results obtained in this study indicate that the levels of cholinesterases within CSF are abnormal in demented patients. Acetylcholinesterase activity is reduced in ventricular CSF of patients exhibiting the clinical and histological features of Alzheimer's disease and in the lumbar CSF of patients with dementia of non-Alzheimer aetiology. A pronounced reduction in nsChE activity and an altered ratio of AChE/nsChE activity also occurs in ventricular and lumbar CSF of SDAT patients.

These biochemical abnormalities are not artefacts arising from drug treatment. Only 27% of the clinically diagnosed patients in the lumbar CSF study were on psychoactive drugs, and only one of these was receiving an antipsychotic phenothiazine drug, whereas all the histologically diagnosed patients in the lumbar CSF study were drug-free. Drug treatment also seems an unlikely explanation for the lower AChE levels observed in the ventricular CSF of patients with Alzheimer's disease as the medication for both these patients and the control group was not very different. For example the mean AChE level of the 3 patients in the control group who were receiving antipsychotic drugs was 21.5 mU/ml compared with a mean level of 4.3 mU/ml in the 3 SDAT patients who were receiving similar drugs.

There is a possibility that the apparent decreases in the AChE activity of ventricular CSF in SDAT patients is a postmortem artefact since many Alzheimer's disease patients die in a cachetic state (Hardy *et al.*, 1985a) and it is difficult to select adequate control groups for this particular variable. A prolonged agonal phase before death is known to cause biochemical changes in the brain (Hardy *et al.*, 1985b) which could presumably be reflected in the CSF. However, it is unlikely in the present study that the differences are due to postmortem delay or storage time before assay since these were similar for all the groups and did not correlate with the levels of AChE, nsChE or protein. It would therefore appear that the alterations in cholinesterase levels of CSF from demented patients are a real feature of the disease process itself.

*Possible relevance of CSF acetylcholinesterase to the disease process*

A markedly lower AChE activity of ventricular CSF was observed in patients dying with Alzheimer's disease. This phenomenon was restricted to those patients with Alzheimer's disease, with normal levels of AChE being observed in patients with dementia of non-Alzheimer aetiology, Parkinson's disease and depression. Despite the lack of a significant correlation between the decrease in AChE activity and the severity of the dementia, as determined by cortical plaque and tangle counts, it does appear to be related to the disease process as the 2 patients with clinically mild dementia and normal cortical ChAT levels did not exhibit a deficit of AChE activity in their CSF.

The protein content of ventricular CSF followed a similar pattern so that it was

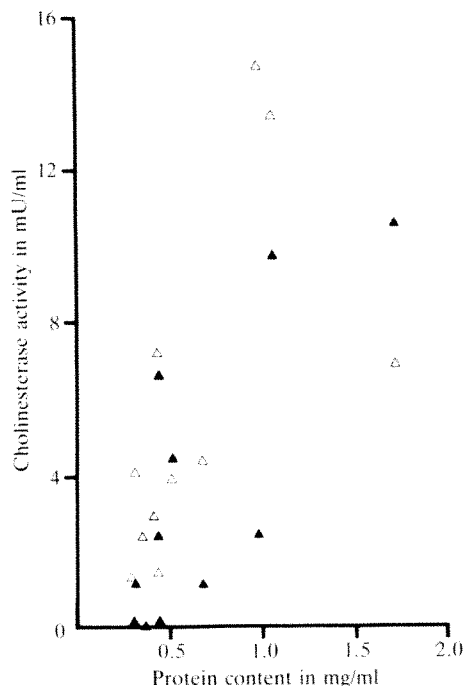


FIG. 2. Correlation between acetylcholinesterase and nonspecific cholinesterase activities with protein content in ventricular CSF from patients with Alzheimer's disease diagnosed at postmortem. Open triangles = acetylcholinesterase activity ( $r = 0.70$ ,  $n = 11$ ,  $P < 0.02$ ); filled triangles = nonspecific cholinesterase activity ( $r = 0.668$ ,  $n = 11$ ,  $P < 0.05$ ). Cholinesterase activities are expressed as nmol acetylthiocholine hydrolyzed/min/ml CSF.

significantly correlated with the AChE activity in SDAT patients (fig. 2), and the mean specific activity of AChE (expressed per mg protein) was below that of controls (Table 3). It is possible that these decreases in AChE activity and protein content are the result of dilution of the CSF due to the enlarged ventricular volume of SDAT patients (De Leon *et al.*, 1980; Soininen *et al.*, 1982). Alternatively, the lowered protein content of the ventricular CSF could be a consequence of the reported decreased protein synthetic ability of nerve cells in Alzheimer's disease (Mann *et al.*, 1981); indeed reductions in specific brain proteins such as soluble tubulin have been reported in SDAT patients (Kosik *et al.*, 1982; Borthwick *et al.*, 1985). If the latter is the case, then the lowered levels of AChE in ventricular CSF that are observed in the SDAT patients are the result of reduced secretion from the brain. The AChE activity of ventricular CSF is presumably derived from those areas of the brain that are close to the ventricular space, including the cortex and hippocampus, both of which are profoundly affected in Alzheimer's disease (but not in other dementias; Perry *et al.*, 1978) with widespread decreases in AChE activity occurring in all cortical and hippocampal regions (Davies, 1979). Acetylcholinesterase is secreted from the rat hippocampus (Appleyard and Smith, 1985), and this secretion would presumably also be decreased in SDAT patients, resulting in a lowered level of AChE in ventricular CSF. In addition, the form of AChE secreted from the brain is abnormal in patients with SDAT and is no longer subject to substrate inhibition which must have profound consequences on the function of the enzyme.



In contrast, normal levels of AChE, exhibiting normal kinetic behaviour, were observed in lumbar CSF of SDAT patients. In animal studies the AChE activity of cisternal CSF is higher than that of ventricular CSF (Greenfield, 1977) suggesting that brain structures caudal to the ventricular system make a significant contribution to the secreted AChE present in cisternal CSF. A similar situation exists in humans: the lack of a rostrocaudal gradient of AChE activity indicates a diffuse origin of the AChE in lumbar CSF, including the spinal cord (Johnson and Domino, 1971; Lal *et al.*, 1984). Contributions from these regions to the AChE in lumbar CSF could therefore mask any changes occurring in ventricular CSF. Acetylcholinesterase is widely distributed in human spinal cord and is present in cholinergic motor neurons (Houser *et al.*, 1983; Barber *et al.*, 1984). However, to date no studies have examined levels of AChE and ChAT in the spinal cord of SDAT patients, although it has been reported that motor neurons are unaffected in Alzheimers' disease (Davies, 1983; Hardy *et al.*, 1985a). The fact that the AChE activity of lumbar CSF is normal suggests that the spinal cord is not affected by this disease. This is probably not the case in dementia of non-Alzheimer aetiology since such patients exhibited decreased levels of AChE activity in lumbar, but not ventricular, CSF indicating decreased secretion of the enzyme from the spinal cord.

*Nonspecific cholinesterase/butyrylcholinesterase activities of CSF from alzheimer's disease patients*

The only consistent change found in all SDAT patients studied was a lower level of nsChE and BuChE activity in the CSF. This parameter also distinguished the SDAT patients from those with other dementias (except pseudodementia) since no decreases were observed in the CSF of these patients. This phenomenon is also responsible for an increased ratio of AChE/nsChE or AChE/BuChE activities in all the SDAT patients, even in ventricular CSF, and again this effect is specific for Alzheimer's disease (and pseudodementia).

Butyrylcholinesterase is present in the brain (*see* Silver, 1974) and biochemical studies have demonstrated that the regional variation of BuChE activity is less than that of AChE with comparatively higher levels of BuChE activity occurring in white matter (Cavanagh *et al.*, 1954). Histochemical studies have shown that BuChE is mainly located in glial cells (Koelle, 1954), but it is also present in nerve cells (e.g., Graybiel *et al.*, 1982) with exceptionally high activity being observed in a few selected nuclei, which are species-dependent (Friede, 1967). In man BuChE is present in neurons in the subependymal tissue near the nucleus of the solitary tract, the dorsal vagus nucleus and the tissue around the central spinal canal. However, very little BuChE is observed in the cerebral cortex and hippocampus, areas in which increased level of BuChE has been reported in Alzheimer's disease (Perry *et al.*, 1978).

No studies have yet been performed to determine whether BuChE can be secreted from these brain regions, or from glial cells, and the relationship between the decreased levels of BuChE in lumbar CSF and the increased brain tissue levels of

SDAT patients is therefore uncertain. The function of BuChE within the brain is not yet known (*see* Silver, 1974; Kutty, 1980) and the significance of these alterations in BuChE activity in the disease process is unclear. Despite these uncertainties, however, it would appear that estimation of BuChE activity and/or the AChE/BuChE ratio in lumbar CSF may prove a valuable diagnostic aid in Alzheimer's disease.

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*Note added in proof.* Similar changes in the BuChE content of lumbar CSF in Alzheimer's disease have been reported by Heff *et al.* (1986) *Journal of the Neurological Sciences*, **72**, 121–129.

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# SUPRASPINAL CONTROL OF MOTONEURONS INNERVATING THE STRIATED MUSCLES OF THE PELVIC FLOOR INCLUDING URETHRAL AND ANAL SPHINCTERS IN THE CAT

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## SUMMARY

The nucleus of Onuf (ON) in mammals contains motoneurons innervating the pelvic floor muscles including the external urethral and anal sphincters. Recently, direct pathways from the dorsolateral pons to the ON, probably involved in supraspinal micturition control, have been reported (Holstege *et al.*, 1986). Since the pelvic floor muscles are involved not only in micturition but also in various other functions (e.g., coughing, vomiting, defaecation, parturition), an attempt has been made to establish whether, in the cat, there exist other direct brainstem pathways to the ON motoneurons. Our results indicate that specific projections to the ON are derived from 3 different areas: (1) the ipsilateral paraventricular hypothalamic nucleus; (2) the ipsilateral caudal pontine lateral reticular formation; and (3) the contralateral caudal nucleus retroambiguus. More diffuse projections (to all motoneuronal cell groups in the spinal cord including the ON) are derived from (1) neurons in the area of the nucleus subcoeruleus in the dorsolateral pontine reticular formation, (2) the nucleus raphe pallidus, and (3) the ventral part of the medullary medial reticular formation. Possible functional implications of these pathways are discussed.

## INTRODUCTION

As early as 1899 Onufrowicz, calling himself Onuf, described a group X in the ventral horn of the human sacral spinal cord, extending from the caudal S1 to the rostral S3 segments. The motoneurons in this nucleus were characterized by their relatively small size and rather densely packed arrangement. He suggested that in the male the motoneurons in this group innervate striated muscles involved in the acts of erection and ejaculation. He also suggested that these motoneurons innervate the urethral and anal sphincters, although this was not his final conclusion. More recently, Mannen *et al.* (1977) studied the sacral spinal cords of patients who had died from amyotrophic lateral sclerosis (ALS) and noticed that, in contrast to the other somatic motoneurons in the sacral cord, the motoneurons in the nucleus of

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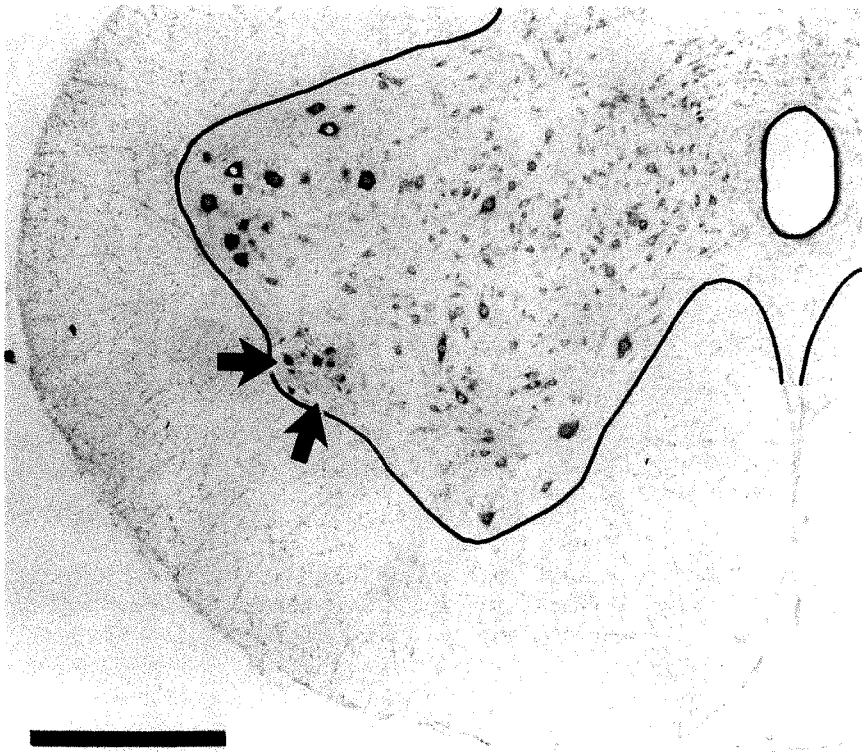


FIG. 1. Brightfield photomicrograph of the ventral horn of a section through the left ventral horn of the S1 spinal segment in the cat. The arrows indicate the nucleus of Onuf. Bar = 1 mm.

Onuf (ON) were well preserved. The autonomic (parasympathetic) motoneurons in the sacral cord, which innervate the detrusor muscle and the internal urethral sphincter, were also spared. Furthermore, it is well known that in most ALS patients the functions of the bladder, its sphincters and the anal sphincters remain intact until the latest stages of the disease. Combination of these findings led to the conclusion that motoneurons in the ON innervate the striated muscles of urethral and anal sphincters (Mannen *et al.*, 1977).

Homologues of ON have been described in the rat (Schröder, 1980), rabbit (Nagashima *et al.*, 1979), cat (Romanes, 1951), dog (Petras and Cummings, 1978) and squirrel monkey (Nakagawa, 1980). In the cat, the cell column Y of Romanes (1951) is homologous to ON. This cell group (fig. 1) is located in the caudal half of the first and in the rostral half of the second sacral segment and its motoneurons innervate, via the pudendal nerve, the striated muscles of the pelvic floor, including the urethral and anal sphincters (Sato *et al.*, 1978; Kuzuhara *et al.*, 1980; Ueyama *et al.*, 1984).

In mammals, the urethral and anal sphincters play an important role in micturition and defaecation. Patients with transverse lesions of the spinal cord above sacral levels usually develop dyssynergia of the detrusor and external urethral

TABLE. HORSERADISH PEROXIDASE (HRP) INJECTIONS INTO MUSCLE

| <i>Cat</i> | <i>Muscles injected</i>    | <i>Amount of injected HRP dissolved in saline</i> |
|------------|----------------------------|---------------------------------------------------|
| 1668       | Detrusor muscle of bladder | 60 $\mu$ l, 10% (Miles)                           |
| 1678       | Bulbar part of urethra     | 35 $\mu$ l, 10% (Miles)                           |
| 1762       | Levator ani                | 30 $\mu$ l, 20% (Boehringer)                      |
|            | External anal sphincter    | 30 $\mu$ l, 20% (Boehringer)                      |
|            | Levator scroti             | 40 $\mu$ l, 20% (Boehringer)                      |
| 1815       | Urethral sphincter         | 20 $\mu$ l, 20% (Boehringer)                      |

sphincter muscles, indicating that the coordination of these muscles takes place at supraspinal levels (Blaivas, 1982). This suggests that there exist direct brainstem projections to ON. In the cat, direct projections from supraspinal levels to spinal motoneurons (including those of ON) could not be demonstrated by lesion-degeneration studies using silver impregnation techniques (Nyberg-Hansen, 1969). Modern anterograde tracing techniques, however, such as the autoradiographic tracing method, have revealed a direct pathway from the dorsolateral pontine reticular formation to ON (Holstege *et al.*, 1979; Holstege and Kuypers, 1982). This pathway may play a role in micturition control (Holstege *et al.*, 1986). Since the pelvic floor is involved not only in micturition but also in other functions (Floyd and Walls, 1953), the question arises as to whether there exist direct projections to ON derived from supraspinal structures other than the dorsolateral pontine reticular formation. In this study, therefore, an attempt was made to reveal all diencephalic and brainstem connections to ON. The results show several such projections, which probably form the neuroanatomical substrate of the various different functions of the pelvic floor, including its sphincters.

## MATERIALS AND METHODS

### *Horseradish peroxidase studies*

In order to discover whether the motoneurons that innervate different parts of the pelvic floor are located in different parts of the nucleus of Onuf (ON), injections of horseradish peroxidase HRP were made as follows. In a male cat (no. 1678), under pentobarbitone sodium (Nembutal) anaesthesia, HRP dissolved in saline was injected into the muscles of the bladder neck and proximal urethra rostral to the prostate gland, probably not involving the external urethral sphincter. In another male cat (1815) HRP was injected only in the urethral wall at the location of maximum urethral pressure. This point was determined by means of a pressure transducer, mounted on a 4 FG urethral catheter (Holstege *et al.*, 1986), and represents the external urethral sphincter. In a third male cat (1762) HRP was injected into the muscles of the anal sphincter and surrounding musculature. To determine whether or not the ON also contains motoneurons innervating the bladder itself, in 1 male cat (1668) HRP was injected into the wall of the body of the bladder. In the Table the different muscles and the amounts of injected HRP are shown. In a fifth cat (1786) 20  $\mu$ l of a 30% solution of HRP in saline was injected into the grey and white matter of the left half of the S1 spinal segment by means of multiple needle penetrations. In order to verify that the retrogradely labelled neurons distribute their fibres only through the ipsilateral funiculi of the spinal cord, a contralateral hemisection at the level of the L2 spinal segment was made before the HRP injection.

All 5 cats survived for 3 days, after which they were deeply anaesthetized with pentobarbitone sodium and perfused transcardially with, in sequence 2 l of saline at room temperature, 4 l of a fixative solution containing 1% paraformaldehyde and 1.25% glutaraldehyde in 0.2 M phosphate buffer (pH 7.2–7.4) at room temperature, and 2 l of 20% sucrose in 0.2 M phosphate buffer (pH 7.2–7.4) at 4° C.

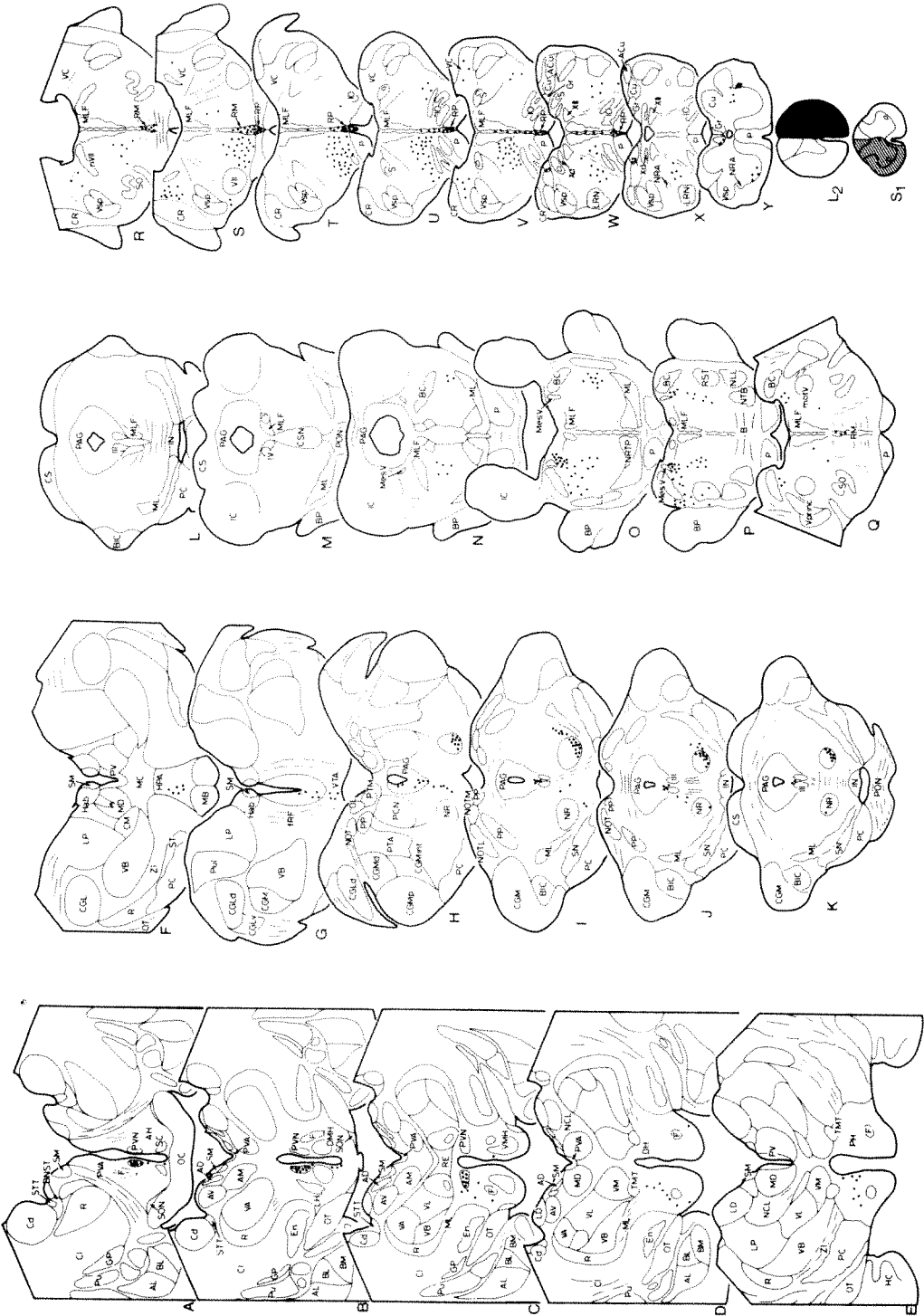


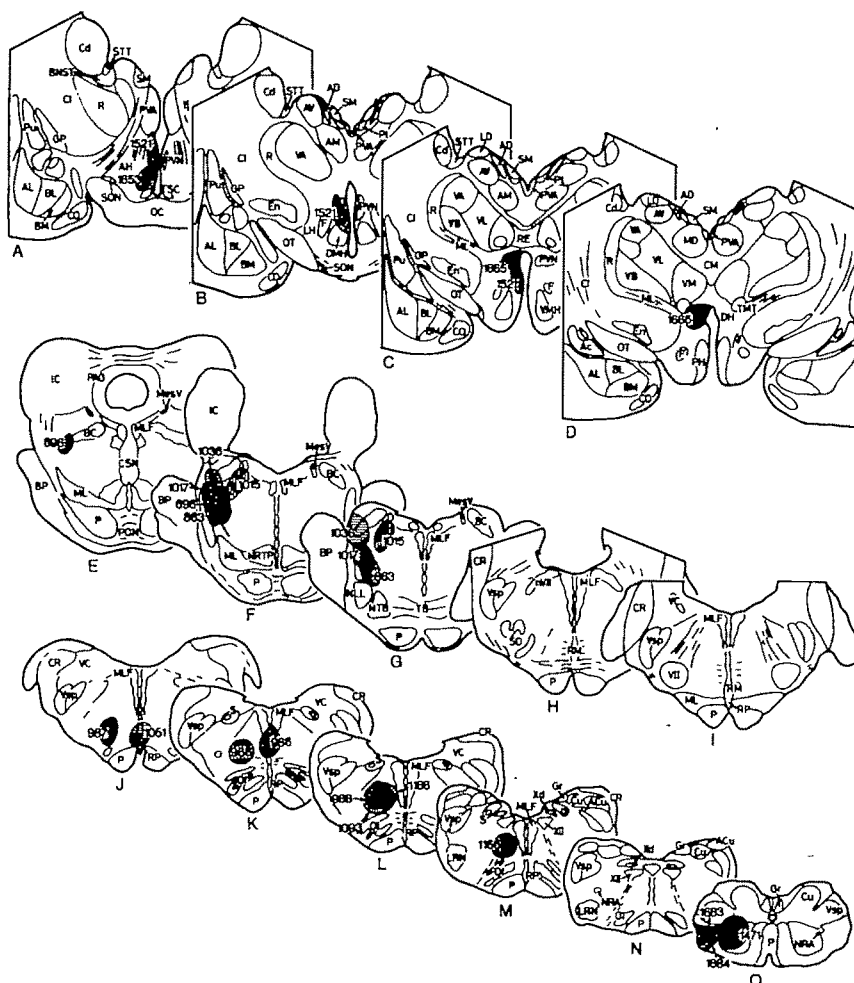
FIG. 2. Schematic drawings of 25 sections through the diencephalon and brainstem illustrating the distribution of HRP-labelled neurons in Cat 1786. A right hemisection at the level of the L2 segment was performed, followed by an HRP injection in the left half of the first sacral segment. For explanation of



In the animals with injections into muscles, only the lumbosacral spinal cord was removed, but in the cat with spinal cord injections the whole brain, brainstem and spinal cord were obtained. They were stored overnight in 30% sucrose 0.2 M phosphate buffer (pH 7.2–7.4) at 4° C and subsequently cut transversely into frozen 30  $\mu$ m thick sections. Every third section was kept in phosphate buffer and incubated a few hours later according to the TMB method of Mesulam (1978). In cat 1786 the resulting pattern of HRP-labelled neurons was plotted. Drawings of brainstem sections at 25 different levels were made to illustrate the distribution of the retrogradely labelled neurons in the diencephalon and brain stem (fig. 2).

#### *Tritiated leucine injections*

Since the retrograde HRP results in cat 1786 (fig. 2) did not reveal whether the HRP labelled neurons in the diencephalon, brainstem and spinal cord projected to ON or to other parts of the sacral spinal cord, the anterograde autoradiographic tracing technique was also used. Areas with neurons that, according to the HRP results, project to the sacral cord were injected with radioactive



tracer. In 52 cats L-[4,5-<sup>3</sup>H] leucine (SA > 100 Ci/mmol) in distilled water was injected with a Hamilton microsyringe fitted with a 22-gauge needle. In all animals 0.5 µl containing approximately 50 µCi was injected. After a survival time of 6 weeks the animals were deeply anaesthetized and perfused with saline followed by 10% formalin. This long survival time was chosen, because it has been shown previously in our laboratory that, after 2 weeks' survival following injection of <sup>3</sup>H-leucine in the brainstem, the lumbosacral segments of the spinal cord are only weakly labelled, whereas after 6 weeks' survival a much more pronounced distribution pattern is observed (Holstege *et al.*, 1979). In the same study it was demonstrated that this pronounced distribution pattern was not due to transneuronal transport. The diencephalon, brainstem and spinal cord were postfixed in 10% formalin for at least 1 week, followed by 2 days in a 30% sucrose-10% formalin mixture and then cut into transverse frozen sections, 25 µm thick. They were prepared for autoradiography with Ilford G5 emulsion, exposed for 3 months in the dark and counterstained with cresyl violet (Holstege *et al.*, 1977). The sections were studied under low magnification darkfield illumination and low magnification darkfield photomicrographs were made of the upper sacral cord, using a Wild-Heerbrugg M7S microscope. The injection area in the various experiments was defined as that area in which the silver grains over the cell bodies were as numerous as or more numerous than those over the surrounding neuropil. Actual fibre terminations cannot be demonstrated with light microscopic autoradiography, but we assumed that labelled fibres surrounding motoneurons represented fibres with terminals on these motoneurons. The injection sites in the cases with labelled fibres terminating in ON are shown in fig. 3. Fig. 4 shows drawings of the injection sites of the cats in which no projections to ON were found.

#### Abbreviations

The abbreviations used in figs 2-4 and 7 are as follows.

|        |                                           |     |                                        |
|--------|-------------------------------------------|-----|----------------------------------------|
| ACu    | Accessory cuneate nucleus                 | CO  | Cortical amygdaloid nucleus            |
| AD     | Anterodorsal nucleus of the thalamus      | CR  | Restiform body                         |
| AH     | Anterior hypothalamic area                | CS  | Superior colliculus                    |
| AL     | Lateral amygdaloid nucleus                | CSN | Nucleus centralis superior             |
| AM     | Anteromedial nucleus of thalamus          | Cu  | Cuneate nucleus                        |
| AV     | Anteroventral nucleus of thalamus         | DH  | Dorsal hypothalamic area               |
| BC     | Brachium conjunctivum                     | DMH | Dorsomedial hypothalamic nucleus       |
| BIC    | Brachium of the inferior colliculus       | En  | Entopeduncular nucleus                 |
| BL     | Basolateral amygdaloid nucleus            | F   | Fornix                                 |
| BM     | Basomedial amygdaloid nucleus             | fRF | Fasciculus retroflexus                 |
| BNST   | Bed nucleus of the stria terminalis       | GP  | Globus pallidus                        |
| BP     | Brachium pontis                           | Gr  | Gracile nucleus                        |
| Cd     | Caudate nucleus                           | Hab | Habenular nucleus                      |
| CGL    | Lateral geniculate body                   | HC  | Hippocampus                            |
| CGLd   | Lateral geniculate body, dorsal part      | HPA | Posterior hypothalamus area            |
| CGLv   | Lateral geniculate body, ventral part     | IC  | Inferior colliculus                    |
| CGM    | Medial geniculate body                    | IN  | Interpeduncular nucleus                |
| CGMd   | Medial geniculate body, dorsal part       | IO  | Inferior olive                         |
| CGMint | Medial geniculate body, interior division | LD  | Nucleus lateralis dorsalis of thalamus |
| CGMp   | Medial geniculate body, principal part    | LH  | Lateral hypothalamic area              |
| CI     | Internal capsule                          | LP  | Lateral posterior complex              |
| CM     | Centromedian thalamic nucleus             | LRN | Lateral reticular nucleus              |
|        |                                           | MB  | Mammillary body                        |
|        |                                           | MC  | Nucleus medialis centralis of thalamus |

|      |                                          |        |                                                     |
|------|------------------------------------------|--------|-----------------------------------------------------|
| MD   | Nucleus medialis dorsalis of thalamus    | PV     | Periventricular nucleus of thalamus                 |
| MesV | Mesencephalic trigeminal tract           | PVA    | Paraventricular nucleus of thalamus (anterior part) |
| ML   | Medial lemniscus                         | PVN    | Paraventricular hypothalamic nucleus                |
| MLF  | Medial longitudinal fascicle             | R      | Reticular nucleus of thalamus                       |
| MotV | Motor trigeminal nucleus                 | RE     | Nucleus reuniens of thalamus                        |
| NCL  | Nucleus centralis lateralis of thalamus  | RM     | Nucleus raphe magnus                                |
| NLL  | Nucleus of the lateral lemniscus         | RP     | Nucleus raphe pallidus                              |
| NOT  | Nucleus of the optic tract               | RST    | Rubrospinal tract                                   |
| NOTL | Nucleus of the optic tract, lateral part | S      | Solitary complex                                    |
| NOTM | Nucleus of the optic tract, medial part  | SC     | Suprachiasmatic nucleus                             |
| NR   | Red nucleus                              | SM     | Stria medullaris                                    |
| NRA  | Nucleus retroambiguus                    | SN     | Substantia nigra                                    |
| NRTP | Nucleus reticularis tegmenti pontis      | SO     | Superior olivary complex                            |
| NTB  | Nucleus of the trapezoid body            | SON    | Supraoptic nucleus                                  |
| nVII | Facial nerve                             | ST     | Subthalamic nucleus                                 |
| OC   | Optic chiasm                             | STT    | Stria terminalis                                    |
| OL   | Olivary pretectal nucleus                | TB     | Trapezoid body                                      |
| ON   | Nucleus of Onuf                          | TMT    | Mammillothalamic tract                              |
| OT   | Optic tract                              | VA     | Ventroanterior nucleus of thalamus                  |
| P    | Pyramidal tract                          | VB     | Ventrobasal complex of thalamus                     |
| PAG  | Periaqueductal grey matter               | VC     | Vestibular complex                                  |
| PC   | Cerebral peduncle                        | VL     | Ventrolateral complex of thalamus                   |
| PCN  | Nucleus of the posterior commissure      | VM     | Ventromedial nucleus of thalamus                    |
| PH   | Periventricular hypothalamic complex     | VMH    | Ventromedial hypothalamic nucleus                   |
| PON  | Pontine nuclei                           | VTA    | Ventral tegmental area of Tsai                      |
| PP   | Posterior pretectal nucleus              | ZI     | Zona incerta                                        |
| Pt   | Parataenial nucleus of thalamus          | III    | Oculomotor nucleus                                  |
| PTA  | Anterior pretectal nucleus               | IV     | Trochlear nucleus                                   |
| PTM  | Medial pretectal nucleus                 | Vprinc | Principal trigeminal nucleus                        |
| Pu   | Putamen                                  | Vsp    | Spinal trigeminal complex                           |
| Pul  | Pulvinar                                 | VI     | Abducens nucleus                                    |
|      |                                          | VII    | Facial nucleus                                      |
|      |                                          | Xd     | Dorsal vagal nucleus                                |
|      |                                          | XII    | Hypoglossal nucleus                                 |

## RESULTS

### *HRP injections in the muscles of bladder and pelvic floor*

In Cat 1678, with an injection in the muscle of the proximal urethra and extending into the bladder neck, many HRP-labelled neurons were observed in the ventrolateral part of ON and a few in the parasympathetic intermediolateral cell column of the S2 and S3 spinal segments. Interestingly, a few HRP-labelled neurons could also be observed in the area between ON and the intermediolateral cell column. In Cat 1815, with a more precise injection in the urethral striated external

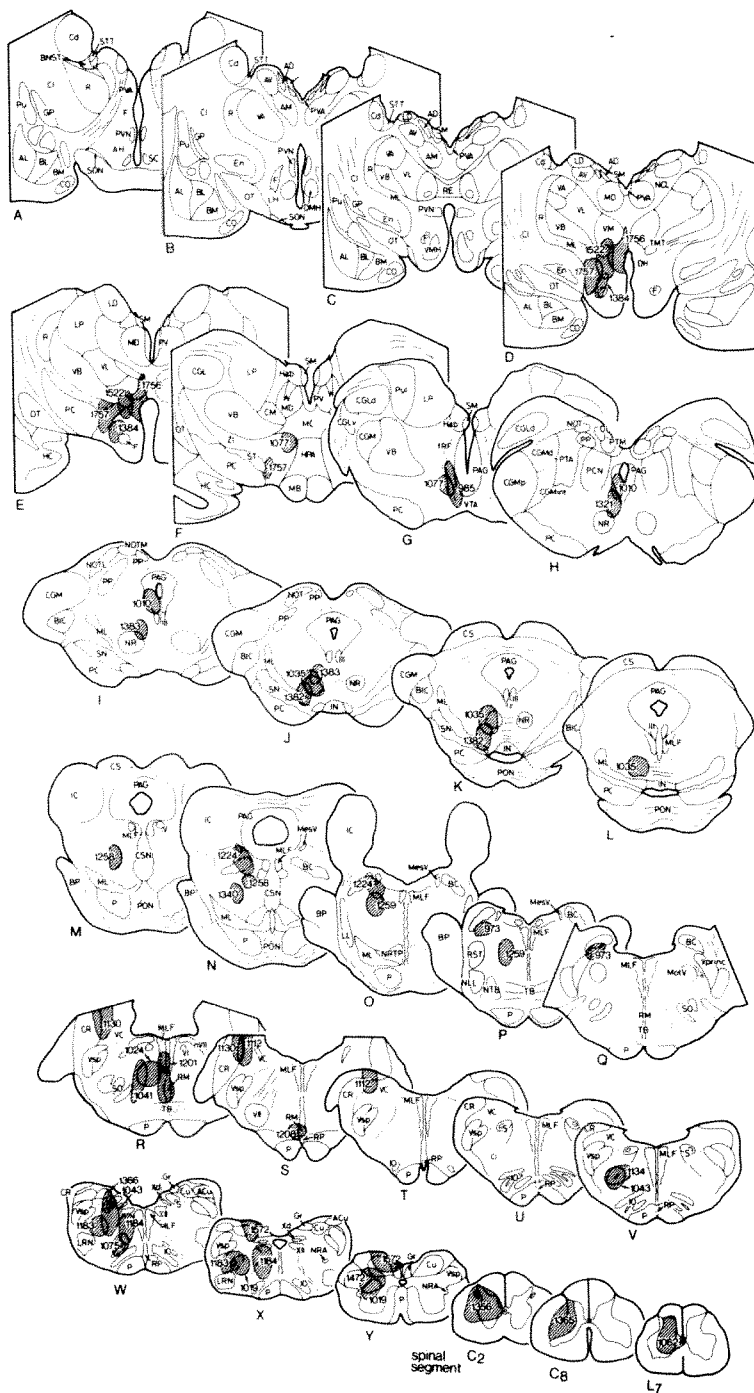


FIG. 4. Schematic drawings of 28 sections through diencephalon, brainstem and spinal cord illustrating the  $^3\text{H}$ -leucine injection sites not giving rise to labelled fibres in the nucleus of Onuf.

sphincter, labelled motoneurons were mainly present ventrolaterally in the ON. In Cat 1762 with HRP injections in the anal sphincter and the surrounding area labelled neurons were found mainly in the dorsomedial part of the ON. In Cat 1668, in which the bladder wall was injected with HRP, many labelled neurons were found in the sacral intermediolateral cell column at the level of spinal segments S2 and S3 but not in the ON. These results indicate that motoneurons in the dorsomedial part of the ON primarily innervate the external anal sphincter and surrounding muscles. Motoneurons in the ventrolateral ON innervate primarily the muscle of the external urethral sphincter. The sacral parasympathetic motoneurons do not innervate the muscles of the external urethral or anal sphincter.

#### *HRP injection in the sacral spinal cord*

In Cat 1786, with a hemi-infiltration of HRP in the S1 spinal segment, labelled neurons were observed in laminae VIII (mainly contralaterally) and X (mainly ipsilaterally throughout the length of the spinal cord). In the most caudal parts of the medulla oblongata, labelled neurons were present ipsilaterally in the ventral part of the reticular formation. Contralaterally they were observed in the caudal nucleus retroambiguus (NRA) and a few were scattered in the lateral reticular formation just dorsomedially to the caudal NRA (fig. 2Y). At the level just caudal to the obex (fig. 2X), labelled neurons were present ipsilaterally in the ventral part of the reticular formation and in the gracile nucleus. No labelled neurons were observed on the contralateral side. At upper medullary levels (fig. 2S–W), many labelled neurons were observed in the raphe nuclei (obscurus, pallidus and magnus), in the ventral part of the medial reticular formation, in the lateral vestibular nuclei (mainly ipsilaterally) and in the inferior vestibular nuclei (bilaterally). At caudal pontine levels (fig. 2Q, R), some labelled neurons were situated in the ipsilateral caudal pontine medial reticular formation. Rostrally to this level (fig. 2P) many labelled neurons were present bilaterally in the area just ventral and medial to the mesencephalic trigeminal tract, probably representing the M-region of Holstege *et al.* (1986) and in the lateral part of the pontine medial reticular formation. Some labelled neurons were found also in the nucleus subcoeruleus and in the area of the Kolliker-Fuse nucleus and ventrally adjacent tegmentum. At upper pontine levels (fig. 2N–P), labelled neurons were situated in the ipsilateral pontine medial reticular formation and in the contralateral pontine lateral reticular formation. In the caudal mesencephalon (fig. 2L, M), labelled neurons were very scarce, but at rostral mesencephalic levels (fig. 2H–K), many were observed mainly contralaterally in the ventrolateral red nucleus. Some others were located ipsilaterally in the Edinger-Westphal nucleus (fig. 2H–J) and the ventral part of the rostral periaqueductal grey matter (PAG) and a few in the ventral tegmental area of Tsai (VTA) (fig. 2G). The labelled neurons in the PAG were noticeably larger than those in the area of the VTA. The group of labelled neurons in the rostral PAG was continuous with the group of neurons in the dorsomedial part of the caudal hypothalamic area (fig. 2E, F). Some labelled neurons were also found in the

lateral hypothalamic area (fig. 2C–E), mainly ipsilaterally. More rostrally in the hypothalamus (fig. 2A–C), many labelled neurons were situated in the paraventricular hypothalamic nucleus (PVN) and a limited number throughout the lateral and periventricular hypothalamic area (fig. 2A, B). Many labelled neurons were located in the motor cortical areas, but the corticospinal projections are beyond the scope of this report.

### *Autoradiographic tracing*

In 52 cats,  $^3\text{H}$ -leucine injections were made in those areas of the spinal cord, brainstem and diencephalon, in which neurons retrogradely labelled with HRP were found after HRP injection in the S1 segment (Cat 1786). The autoradiographic results were subdivided into six groups: (1) hypothalamus, (2) mesencephalon, (3) pons, (4) upper medulla oblongata, (5) caudal medulla oblongata, and (6) spinal cord.

*Injections in the hypothalamus.* In 8 cats (985, 1077, 1384, 1521, 1653, 1665 and 1756) injections were made in this area. Labelled fibres were traced to ON only in those cats in which the injection involved the PVN, (nos 1521, 1653 and 1665). In Cat 1521 the injection site involved major parts of the PVN and directly adjoining areas (fig. 3A–C). The injection site in cat 1653 involved only the rostral part of the PVN (fig. 3A) and rostrally and ventrally adjoining hypothalamic areas. In Cat 1665 (fig. 3C, D), the injection was made more caudally, involving the caudal hypothalamus but extending into the caudal PVN.

In these 3 cats labelled fibres descended laterally through the mesencephalon, pons and ventrolaterally through the medulla oblongata. They descended further in the lateral funiculus throughout the length of the spinal cord (*see also* Holsteg, 1987). From this fibre bundle, labelled fibres were distributed to autonomic motoneurons in the brainstem (dorsal vagal motor nucleus, containing parasympathetic motoneurons) and the spinal cord (thoracolumbar and sacral intermediolateral cell column, containing sympathetic and parasympathetic motoneurons respectively). Labelled fibres were also very numerous in the ON, mainly ipsilaterally (figs 5, 6A). Interestingly, labelled fibres were also distributed to the cell bridge between ON and the sacral intermediolateral cell column.

In the other 5 cats (985, 1077, 1384, 1522, 1756), with injection sites involving the posterior and dorsal hypothalamus and the rostral mesencephalon but not extending into the PVN (fig. 4D–G), no labelled fibres were found in ON. Combining these results with the HRP findings in cat 1786 strongly suggests that the hypothalamic projections to ON are derived from the PVN alone.

*Injections in the mesencephalon.* In 5 cats, injections were made in the interstitial nucleus of Cajal and adjoining mesencephalic tegmentum (1321), the rostral periaqueductal grey (1010) and various parts of the caudal red nucleus (1035, 1382, 1383). Although, according to the HRP results, these areas project to the sacral cord, in none of these cases were labelled fibres distributed to ON.

*Injections in the pons.* In 11 cats (696, 863, 973, 1015, 1017, 1036, 1224, 1235,

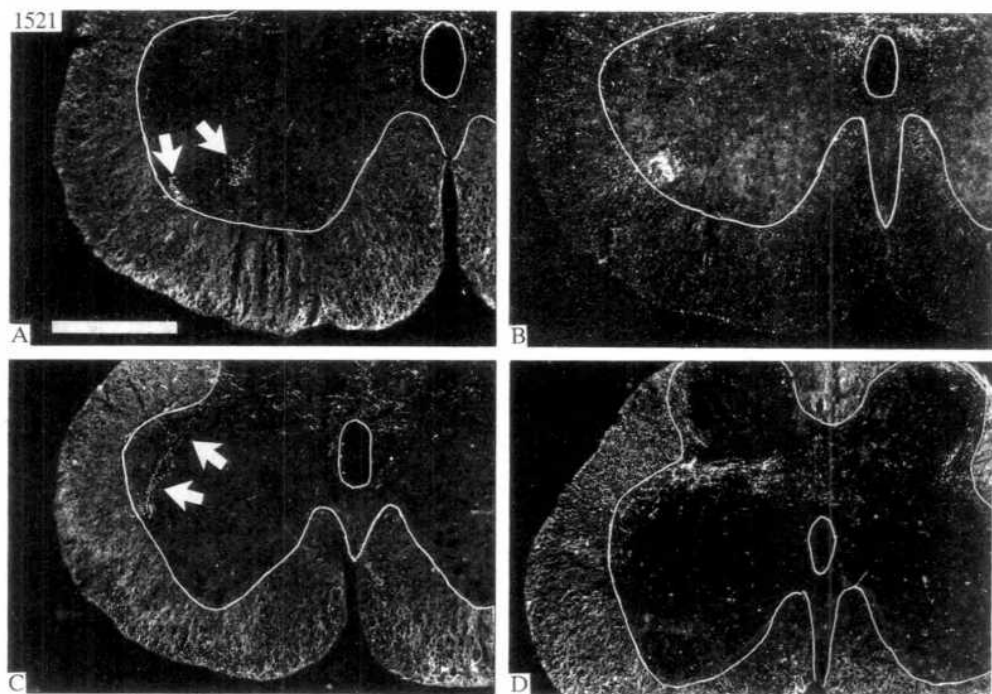


FIG. 5. Darkfield photomicrographs of the S1 and S2 sections in Cat 1521 with a  $^3\text{H}$ -leucine injection in the area of the paraventricular hypothalamic nucleus. Note in A and B the projection to the nucleus of Onuf. In the rostral S1 segment (A) this nucleus consists of two separate cell groups (arrows). Note in C a projection to the cellular bridge between ON and sacral parasympathetic motoneurons (arrows). D shows the projections to the sacral intermediomedial and intermediolateral cell groups. Bar = 1 mm.

1258, 1259, 1340) injections were made in this area. Labelled fibres were traced to ON in only 5 cats (696, 863, 1015, 1017, 1036; fig. 3E–G). In 2 (696, 863) of these 5 animals, the injections sites were situated in the lateral pontine reticular formation, extending only slightly into the nucleus subcoeruleus and the Kolliker-Fuse nucleus. In cat 1015, the injection site was located more dorsally and involved the nucleus subcoeruleus. In Cats 1017 and 1036, the injections were also made more dorsally than in 696 and 863 but extended more laterally than in 1015. They involved the lateral part of the nucleus subcoeruleus and the parabrachial area including the Kolliker-Fuse nucleus. In all 5 cats, many labelled fibres descended in the lateral reticular formation of caudal pons and medulla and continued into the lateral funiculus throughout the length of the spinal cord. From this fibre bundle, many labelled fibres were distributed to ON, bilaterally but with an ipsilateral preponderance. A complicating factor is that in 3 (1015, 1017, 1036) of the 5 cats the injection sites extended into the nucleus subcoeruleus and ventral parabrachial area. These areas contain many noradrenergic neurons, projecting to all parts of the grey matter (including the motoneuronal cell groups) throughout the length of the spinal cord (Nygren and Olson, 1977). Indeed in these 3 cats, labelled fibres were distributed to all parts of the spinal grey matter, but the projections to ON



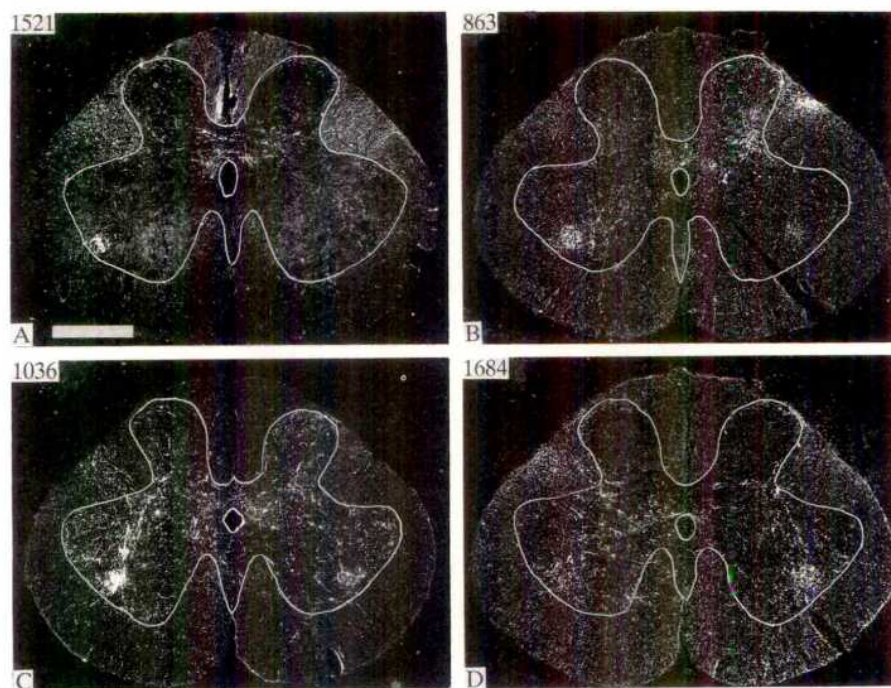


FIG. 6. Darkfield photomicrographs of sections through the S1 segments in Cats 1521 (PVN-injection), 1863 (L-region-injection), 1036 (L-region and subcoeruleus injection) and 1684 (injection in the caudal nucleus retroambiguus). Bar = 1 mm.

were much more pronounced than those to the other somatic motoneuronal cell groups (fig. 6c). Similarly strong projections to ON were also found in cats 696 and 863 (fig. 6b), but in these 2 animals the injection sites extended only slightly or not at all into the nucleus subcoeruleus or ventral parabrachial area. In conclusion, the findings in these 5 cats suggest that there exist two separate pathways from the dorsolateral pontine reticular formation to ON. One is a specific pathway, while the other forms part of a general projection system, probably derived from noradrenergic neurons and involving all parts of the spinal grey matter.

In Cat 1235 (fig. 7), with an injection in the same area as in the first 5 animals of this group, no labelled fibres were found in the ON. However, before the injection of  $^3\text{H}$ -leucine, an ipsilateral hemisection was performed at the C2 spinal level. This indicates that the pathway, from the dorsolateral pontine reticular formation to ON, descends ipsilaterally through the spinal cord. In another cat (1224, fig. 4N, o), the injection was made into the medial part of the dorsolateral pontine reticular formation. In this animal only a few labelled fibres were traced bilaterally to ON. These fibres probably represent subcoeruleospinal fibres. In this same case, an extremely pronounced projection was present to the sacral intermediomedial and intermediolateral cell column. These fibres were most probably derived from the M-region of Holstege *et al.* (1986).

Finally, in Cats 973, 1258, 1259 and 1340 with injections in areas immediately



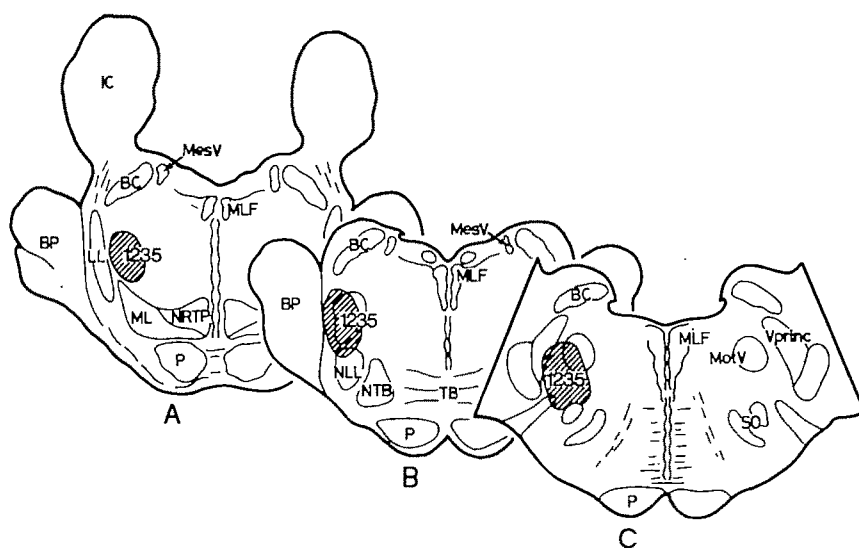


FIG. 7. Schematic drawings of 3 sections through the caudal pons, illustrating the  $^3\text{H}$ -leucine injection site in Cat 1235.

adjoining the dorsolateral pontine reticular formation, no labelled fibres were found in ON. This indicates that the pontine reticular projections to ON are derived only from its dorsolateral portion at levels just rostrally to the motor trigeminal nucleus.

*Injections in the upper medulla oblongata.* In 16 cats injections were made in this area. In 4 (986, 1051, 1201, 1208), the injections were centred on the raphe nuclei but extended into the adjoining reticular formation. In the 2 caudally injected animals (986, 1051; fig. 3J, K) which involved the nucleus raphe pallidus and obscurus, labelled fibres descended in the ventral and lateral funiculi of the spinal cord and many were distributed to all somatic and autonomic motoneuronal cell groups throughout the length of the spinal cord, including ON (fig. 8B). In the other 2 cats (1201, 1208), in which the injections were more rostrally placed (fig. 4R, s), no labelled fibres were found in ON.

In 4 cats (987, 988, 1093, 1166), the injection sites were located in the medullary medial reticular formation at levels between the facial and hypoglossal nuclei (fig. 3J–M). In these 4 cats labelled fibres descended through the ventral and ventrolateral funiculi of the spinal cord and many were distributed to all somatic and autonomic motoneurons including some to ON (fig. 8A).

In the remaining 8 cats of this group (1024, 1041, 1043, 1075, 1112, 1130, 1134, 1184; fig. 4R–X), no labelled fibres were found in ON. This indicates that in the upper medulla oblongata only the caudal raphe nuclei and the adjoining ventromedial reticular formation at the level between the facial and hypoglossal nuclei project to ON (as well as to all other motoneurons in the spinal cord).

*Injections in the caudal medulla oblongata.* In 8 cats (1019, 1183, 1366, 1471,

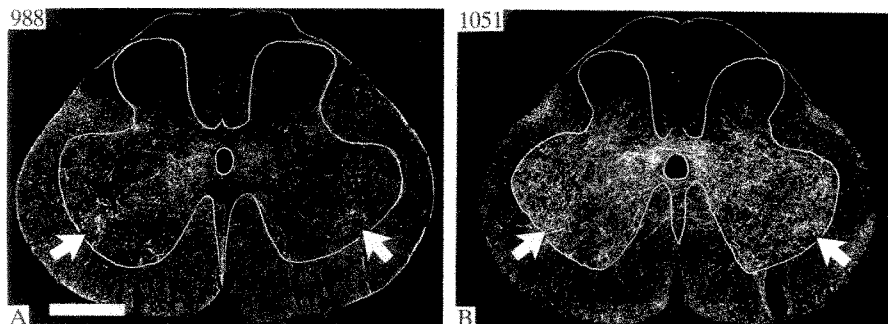


FIG. 8. Darkfield photomicrographs of a section through the S1 segment in Cats 988 (with a  $^3\text{H}$ -leucine injection in the ventromedial part of the medullary medial reticular formation) and 1051 (with a  $^3\text{H}$ -leucine injection in the nucleus raphe pallidus). Note the diffuse projections to the ventral horn including ON (arrows). Bar = 1 mm.

1472, 1572, 1683, 1684), the injection sites were located in the reticular formation at the level of the obex or more caudally. Only in 3 cats (1471, 1683, 1684; fig. 3o) were labelled fibres present in ON (fig. 6D). In 1471 the injection site involved the lateral reticular formation, including the caudal NRA and the most medial part of the caudal spinal trigeminal nucleus. In the other 2 cats (1683, 1684), the bulk of the injection was situated in the white matter of the lateral funiculus but it extended into the caudal NRA and in 1684 also into its immediately adjoining lateral reticular formation.

In these 3 cats two pathways were present, one ipsilateral, descending in the dorsolateral funiculus throughout the length of the spinal cord, the other contralateral, descending in the ventral and ventrolateral funiculi as far as upper sacral levels. From the ipsilateral pathway, labelled fibres were distributed to all parts of the ipsilateral intermediate zone. From the contralateral fibre bundle, labelled fibres were distributed to the abdominal muscle motoneuronal cell groups and to ON, bilaterally but with a contralateral preponderance.

In the other 5 cats (1019, 1183, 1366, 1472, 1572; fig. 4W–Y), injections were placed in the medullary lateral reticular formation just rostral and/or dorsal to the area injected in the first 3 cats of this group. In none of these cases were labelled fibres found in ON. This showed that the parts of the caudal medullary reticular formation projecting to ON are limited to the caudal NRA and the area immediately adjoining it.

*Injections in the spinal cord.* In 3 cats (1356, 1365, 1062), injections were made in the spinal cord at the level of the C2, C8 and L7 segments respectively (fig. 4). In none of them were labelled fibres distributed to ON. The cat with an L7 injection (1062) is especially interesting, because it revealed that many labelled fibres were distributed from the L7 spinal grey to the somatic motoneuronal cell groups in the S1 spinal segment, but none to the ON (fig. 9). Interestingly, in none of the cases in which labelled fibres were traced to ON, a projection especially to the dorsomedial or ventrolateral portions of ON was not noticed. Apparently the hypothalamic

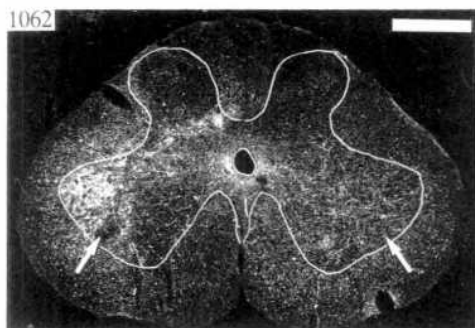


FIG. 9. Darkfield photomicrograph of a section through the S1 segment in Cat 1062 with an injection in the left side of the L7 segment (fig. 4). Note the absence of labelled fibres in the ON (arrow). Bar = 1 mm.

and brainstem structures, which project to ON, have an influence on all pelvic floor musculature and not just part of it.

## DISCUSSION

Our finding that motoneurons in the ventrolateral part of the nucleus of Onuf (ON) innervate the striated urethral sphincter muscles and that motoneurons in the dorsomedial portion of ON innervate the anal sphincter muscles completely corresponds with the observations of Sato *et al.* (1978) and Kuzuhara *et al.* (1980). The existence of a connecting cellular bridge between ON and the sacral intermediolateral cell group has also been reported previously by Rexed (1954), Petras and Cummings (1978), Yamamoto *et al.* (1978) and Nadelhaft *et al.* (1980). This cellular bridge suggests a close connection between the function of the motoneurons in ON which innervate the sphincter muscles, and those in the sacral intermediolateral cell column, which innervate the detrusor muscle of the bladder. Obviously the contractions of the sphincter and detrusor muscles are intimately coordinated during normal bladder filling and micturition. This coordination, however, does not take place at sacral levels, but in the dorsolateral pontine reticular formation (Barrington, 1925; Kuru *et al.*, 1963). Indeed, direct projections from the dorsolateral pontine reticular formation to the sacral parasympathetic motoneurons have been demonstrated in the opossum (Martin *et al.*, 1979), in the rat (Loewy *et al.*, 1979) and in the cat (Holstege *et al.*, 1979, 1982, 1986). Holstege *et al.* (1979, 1982, 1986) also showed direct pathways from the dorsolateral pons to ON. Neurons giving rise to this latter projection were located more laterally (L-region of Holstege *et al.*, 1986) than those projecting to the sacral intermediolateral cell groups (M-region of Holstege *et al.*, 1986). In addition, Holstege *et al.* (1986) demonstrated physiologically that stimulation in the L-region resulted in a rise of urethral pressure and pelvic floor EMG. Stimulation in the M-region, on the other hand, produced a decrease of the urethral pressure and pelvic floor EMG, followed by an increase of the intravesical pressure. This latter pattern also occurs at the beginning of normal micturition.

Fukuda and Fukai (1986) demonstrated in dogs that stimulation in an area of the pontine lateral reticular formation, which resembles the L-region of Holstege *et al.* (1986), produced rhythmic straining. Straining has been defined by Mendeloff (1968) in this context as 'the descent of the diaphragm, closure of the glottis, contraction of the abdominal musculature and tensing of the pelvic floor, leading to an increase in the intra-abdominal pressure involved in defaecatory movements'. In our view this definition of Mendeloff (1968) is relevant not only to defaecatory movements but also to functions such as forced expiration, coughing, sneezing, vomiting and parturition. Obviously the abdominal muscles are essential for increasing the intra-abdominal pressure. However, the only brainstem area projecting specifically to abdominal muscle motoneurons is the area of the nucleus retroambiguus (NRA) in the caudal medulla oblongata (Holstege and Kuypers, 1982; Feldman *et al.*, 1985). The L-region of Holstege *et al.* (1986) does not project directly to abdominal muscle motoneurons (Holstege and Kuypers, 1982). We therefore assume that the rhythmic straining elicited by stimulation in the pontine lateral reticular formation by Fukuda and Fukai (1986) is mediated through neurons in the NRA. In our view, the direct projections from the L-region to ON are mainly involved in the control of micturition. The importance of the area of the NRA in straining is corroborated by the finding of Yamamoto *et al.* (1961) that a tonic increase in abdominal pressure, elicited by stimulation of pelvic afferent fibres, is still present after transection of the medulla just caudal to the obex, but not after more caudal transections.

The NRA is involved in respiratory (Merrill, 1970) and abdominal muscle control (Miller *et al.*, 1985). Merrill (1970) also showed that the caudal part of the NRA is particularly involved in expiratory control, while its rostral part contains neurons related to both inspiration and expiration. This corresponds with the anatomical findings that the rostral NRA projects to both phrenic and abdominal muscle motoneurons, which subserve inspiratory and expiratory movements respectively (Holstege and Kuypers, 1982; Feldman *et al.*, 1985). The caudal NRA does not project to the phrenic nucleus but projects very strongly to abdominal muscle motoneurons (Holstege *et al.*, 1984). In this report we show that the caudal NRA also projects to pelvic floor motoneurons. Therefore stimulation of caudal NRA neurons may elicit simultaneous contraction of the abdominal and pelvic floor muscles or straining behaviour. Floyd and Walls (1953) indicated that the pelvic floor sphincters are contracted in all procedures in which the intra-abdominal pressure is raised with the single exception of defaecation. The direct projection from caudal NRA to ON may be the neuroanatomical substrate of this phenomenon.

The role of the pelvic floor in defaecation is more complex. In the first phase of defaecation, straining, including pelvic floor contraction, occurs, resulting in an increase of the intra-abdominal pressure and also of the intraluminal pressure in the distal colon. As the first portion of the faecal bolus arrives in the upper part of the rectum the external anal sphincter relaxes (Denny-Brown and Robertson, 1935).

The faecal contents are propelled by the high intraluminal pressure brought about by straining movements and emerge with sudden force from the anus (Mendeloff, 1968). The role of the CNS in defaecation has been studied in patients with spinal cord transections. These studies indicated that incontinence for faeces usually occurs only in the first few days or weeks after injury (probably during the spinal shock phase). After this period defaecatory reflexes return to normal, indicating that they are totally vested in the lumbosacral cord. This means that defaecation, with the exception of the straining part of it, is not controlled by supraspinal structures (de Groat *et al.*, 1979).

#### *Nonspecific brainstem spinal pathways*

The dorsolateral pontine reticular formation contains many noradrenergic neurons (Wiklund *et al.*, 1981; Jones and Friedman, 1983). As indicated by Nygren and Olson (1977), noradrenergic fibres derived from the dorsolateral pontine reticular formation terminate in all parts of the spinal grey matter throughout the length of the spinal cord, including the sacral parasympathetic motoneurons and the ON (Kojima *et al.*, 1985). These noradrenergic neurons have a general excitatory influence on all spinal grey structures (White and Neumann, 1980). As already mentioned, the dorsolateral pontine reticular formation also contains micturition control areas (the M and L-regions). In the rat the M-region neurons do not contain noradrenaline (Loewy *et al.*, 1979). The same is probably true for the L-region neurons (*see Results*). This suggests that the dorsolateral pontine reticular formation gives rise to two different projections to ON: a specific one, involved in micturition control, and a noradrenergic one, having a general excitatory influence. As well as the pontine noradrenergic projections, other diffuse direct brainstem projections to ON exist. For example, we found strong projections from the nucleus raphe pallidus and from the ventromedial medullary reticular formation to all somatic and autonomic motoneurons throughout the length of the spinal cord, including those of ON. Such diffuse projections have also been shown by Martin *et al.* (1979) in the opossum, and by Holstege *et al.* (1979) and Holstege and Kuypers (1982) in the cat. The nucleus raphe pallidus contains very many serotonergic neurons (Wiklund *et al.*, 1981), some of which also contain substance P (Hökfelt *et al.*, 1978) and leu-enkephalin (Hökfelt *et al.*, 1979). In the spinal cord many serotonergic fibres and terminals have been observed (Dahlström and Fuxe, 1964, 1965; Steinbusch, 1981). Stimulation of serotonergic fibres may cause facilitation of motoneurons (White and Neumann, 1980).

Significantly, neurons in the ventral part of the medullary medial reticular formation also project diffusely to the spinal motoneuronal cell groups. These neurons contain neither noradrenaline nor serotonin (Wiklund *et al.*, 1981). This indicates that there exist three different descending diffuse projection systems to the spinal motoneurons: (1) a noradrenergic one derived from the dorsolateral pontine reticular formation; (2) a serotonergic one derived from the nucleus raphe

pallidus; and (3) a nonnoradrenergic, nonserotonergic one derived from the ventral part of the medullary medial reticular formation.

#### *Paraventricular nucleus of the hypothalamus*

A specific projection to ON appeared to be derived from the paraventricular hypothalamic nucleus (PVN). The PVN contains a great number of putative neurotransmitters such as vasopressin and oxytocin, somatostatin, dopamine, met-enkephalin, substance P, neurotensin, glucagon, renin, corticotropin releasing factor, and pro-opiocortin-derived peptides (for review, *see* Swanson and Sawchenko, 1983). Moreover, it has been demonstrated that fibres in the ON contain somatostatin (Schröder, 1984; Erdman *et al.*, 1984; Katagiri *et al.*, 1986), neuropeptide Y (Katagiri *et al.*, 1986), leu-enkephalin (de Groat *et al.*, 1983), met-enkephalin, serotonin and substance P (Micevych *et al.*, 1986). Although some of these substances were found, at least partly, to be derived from dorsal and/or ventral roots (Katagiri *et al.*, 1986), the PVN also contributes to the presence of such substances in the ON.

It is only possible to speculate about the function of this direct hypothalamo-ON projection. Some of the muscles innervated by ON motoneurons are involved in sexual activities such as erection and ejaculation. Possibly this PVN-ON projection plays a role in these functions. Furthermore, the PVN, acting through its projection to the hypophysis, can raise the level of oxytocin in the blood, resulting in strong contractions of the uterus in pregnant women. Perhaps the PVN produces not only uterine contractions via the hypophysis and the blood stream, but also pelvic floor contractions by way of its oxytocinergic (?) projections to the ON in the sacral cord.

According to Holstege (1987), the PVN also projects to Rexed's lamina I of the spinal cord (which is involved in pain perception), lamina X and the thoracolumbar sympathetic (Saper *et al.*, 1976; Holstege, 1987) and sacral parasympathetic motoneurons (Holstege, 1987). This combination of projections suggests that the autonomic systems, especially, receive direct hypothalamic afferents. This raises the question whether ON motoneurons belong to the somatic or to the autonomic motor system. This problem has already been discussed extensively (Laruelle, 1937; Rexed, 1954; Sung, 1979; Mannen *et al.*, 1982).

The following arguments favour ON motoneurons being autonomic. (1) Both autonomic and ON motoneurons are unaffected in patients with ALS (Mannen *et al.*, 1977; Iwata and Hirano, 1982). (2) Both autonomic and ON motoneurons receive direct hypothalamic afferents. (3) ON motoneurons have an intimate relationship (anatomical as well as physiological) with sacral parasympathetic motoneurons. (4) Cytoarchitectonically, ON motoneurons more closely resemble autonomic motoneurons than somatic motoneurons (Rexed, 1954). (5) Unlike somatic motoneurons, ON motoneurons seem not to receive afferents from interneurons in the adjacent intermediate zone (*see* fig. 9). On the other hand there are two strong arguments in favour of ON motoneurons having a somatic nature: (1)

ON motoneurons innervate striated musculature; (2) pelvic floor muscles innervated by the ON motoneurons are under voluntary control. Perhaps the ON motoneurons should be considered as neither autonomic nor somatic, but as a special class of motoneurons.

Regardless of the class to which the ON motoneurons belong, our results reveal that they receive afferent information from various different brain stem and diencephalic areas. These areas are involved in divergent functions such as micturition, straining and sexual activities, and their descending pathways to ON form part of the neuroanatomical framework of these important bodily functions.

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# CHANGES OF REGIONAL CEREBRAL BLOOD FLOW MEASURED SIMULTANEOUSLY IN THE RIGHT AND LEFT HEMISPHERE DURING AUTOMATIC SPEECH AND HUMMING

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## SUMMARY

Regional cerebral blood flow (rCBF) was measured simultaneously in both hemispheres during automatic speech and during humming. During automatic speech rCBF increased slightly but significantly more in the right hemisphere. No side difference was found during humming. At rest and in both test situations the rCBF was highest bifrontally. Regional analysis revealed multiple regions of significantly increased rCBF in both hemispheres during both speech and humming. Some of these regions coincided with known speech centres in the left hemisphere. Others, especially on the right, did not. It is concluded that vocal activation during both speech and humming requires a collaboration of the two hemispheres in various functional patterns.

## INTRODUCTION

In 1861 Paul Broca reported his famous patient 'TanTan' who was unable to speak but who had seemingly normal comprehension of words. At autopsy the patient was found to have an infarct involving the triangular and opercular region of the left frontal lobe. Later findings of patients with speech disturbance and lesions in the left hemisphere led Broca (1865) to propose that speech is a function of the left hemisphere. This was supported by the discovery in 1874 by Wernicke of a speech area in the superior posterior part of the left temporal lobe and adjacent parietal regions. A great number of later investigations (*see* Penfield and Roberts, 1959; Levy *et al.*, 1971) have confirmed the dominant role of the left hemisphere for speech functions. The right hemisphere, however, was not found to be entirely lacking in speech-related functions. Especially perception (Faglioni *et al.*, 1969; Heilman *et al.*, 1975), but also production of prosodic qualities of speech (Botez and Wertheim, 1959), which enables expression of the emotional content, has been ascribed to the right hemisphere since it may be altered by right hemisphere lesions.

Also subcortical structures, such as caudate and thalamic regions, have been found to be of importance for speech and for verbal memory (Ojemann 1975, 1978; Metter *et al.*, 1983).

The introduction of the 133-xenon clearance technique to measure regional cerebral blood flow (rCBF) by intra-arterial injections of the isotope (Lassen and Ingvar, 1961, 1972; Lassen *et al.*, 1963) made it possible to study regional functional changes in the brain during speech. By this method augmentation of cortical blood flow concomitant with neuronal activation (Raichle *et al.*, 1976; Greenberg *et al.*, 1979) could be studied. The first studies of rCBF during speech were made by Ingvar and Schwartz in 1974 and by Larsen *et al.* in 1978. These measurements revealed that automatic speech did not especially activate Broca's and Wernicke's areas. The largest flow increases were seen in the supplementary motor area and regions anterior to it in the frontal lobe, the sensorimotor regions for the mouth, as well as in the auditory cortex. Focal increase in blood flow was also seen in the right hemisphere during automatic speech with a similar distribution as on the left side. However, since the intra-arterial rCBF method only permits measurement of one hemisphere at a time, simultaneous measurements of rCBF in the right and the left hemisphere were not possible. With intravenous (i.v.) administration of 133-Xe the radioactive isotope is carried simultaneously to both hemispheres and so enables bilateral rCBF measurements.

In the present i.v. rCBF study we have compared the simultaneous rCBF changes in the right and the left hemisphere, first during automatic speech, and secondly during humming of a simple tune to determine if the nonverbal activation (humming), in contrast to the verbal activation (automatic speech), shows different right and left hemisphere involvement.

## METHODS

### *Subjects*

Fifteen patients (aged 22–69, mean 51 yrs; 9 males and 6 females) volunteered for the study. Group A consisted of 5 patients who more than 3 months previously had suffered 1–2 transient ischaemic attacks (TIA) (4 with a duration of neurological symptoms of less than 12 h, 1 less than 24 h). The neurological deficit during the TIA was in all cases localized to the territory of the internal carotid artery (3 on the right, 2 on the left). One of the patients had a 10 min episode of expressive dysphasia during a single TIA located in the territory of the left carotid artery. Group B consisted of 10 patients suffering from repeated attacks of unilateral amaurosis fugax (4 on the right, 6 on the left). At the rCBF study none of the 15 patients had had any signs of neurological deficit subsequent to their attacks. All patients had normal findings in a routine aphasia test (Token Test). They also had normal CTs, and routine EEG did not show any focal abnormalities or side differences. Routine screening for haemodynamically significant stenosis of the carotid arteries by angiography or Doppler ultrasound gave negative results for all subjects. They were all fully right-handed according to the Edinburgh Inventory and they had no hearing deficit for speech. They were all well informed about the rCBF measurements. In a second group of 14 normal subjects (age 25–52, mean 34 yrs), rCBF measurements were made during inhalation of 6% CO<sub>2</sub> air mixture (n = 8) or during hyperventilation (n = 6) to determine the pCO<sub>2</sub> reactivity of the CBF values.

### *rCBF measurements*

Measurements of rCBF were made with i.v. administration of 1 GBq (25 mCi)  $^{133}\text{Xe}$  dissolved in saline in a cubital vein and extracranial recording with 30 detectors over each hemisphere. In the temporal region the diameter of each detector field was about 2 cm. Localization of the head relative to the detectors was made by light beams on the nasion and the external auditory meatus. This made it possible to control the head position during the measurements within about  $\pm 5$  mm. At each measurement  $^{133}\text{Xe}$  was given through a 20 cm long plastic tube (so as not to alert the subject to the moment of isotope injection) immediately followed by rapid infusion of 20 ml sterile saline. The cortical grey matter blood flow (fg) was calculated by biexponential analysis of the clearance curve (Obirst *et al.*, 1975). A start fit time of 1.0 min was used for the flow analysis. Recording artefacts from  $^{133}\text{Xe}$  in the airways were eliminated by means of quantitative compensation algorithm (Nilsson *et al.*, 1982). Continuous recording of the end tidal  $\text{pCO}_2$  during the rCBF measurements was made by a Siemens Sirecust Capnograph.

In each subject rCBF measurements were made with an interval of 30 min during (1) rest, (2) automatic speech (repetitive recital of the weekdays), and (3) humming (without words) of a simple and well-known nursery rhyme. The measurements were made in the same order (rest, speech, humming) in all subjects. The activations were started 2 min before the rCBF measurements and were continued for 6 min.

### *Statistical methods*

The mean and SD of each regional CBF value were calculated for each group of measurements (rest, speech and humming), and were used for subsequent group comparisons. The significance of the CBF changes was tested by Student's paired *t* test (two-tailed). The interhemispheric correlation between CBF values from corresponding regions in the right and left hemispheres was tested by linear regression. The correlation between the CBF patterns in the right and left hemisphere or between the rCBF patterns at rest, during speech and humming was tested by Spearman's rank correlation of the flow in corresponding detectors. The regional distribution of *t* values was calculated as Student's unpaired *t* test.

The interpretation of the 't maps' into maps of activity correlated rCBF increase, and hence into maps of cortical activation, is an important and complex issue. We have chosen to translate the *t* values into their corresponding probability values according to the *t* probability distribution with 28 deg of freedom. Thus the *t* value needed for a  $P < 0.05$  (one-tailed) CBF increase is at least 1.7. However, in a hemisphere *t* map with 28 regions, for the localization of each activated region to be significant on the  $P < 0.05$  (one-tailed) level, the *P* value for each detector site must be 28 times smaller, which corresponds to a *t* value of at least 3.2. Correspondingly, a pair of adjacent activated regions must each attain a *t* value of at least 2.9. Thus the certainty of a correct localization of the activated regions increases with higher *t* values. On the other hand, if too high a *t* value is chosen for the identification of an activated region, the number of erroneously excluded regions (type II error) will be exaggerated. We have chosen a *t* value of at least 3.0 to identify an activated cortical region, since it gives an acceptable regional localization and a regional type II error that is less than 50%. An activated cortical region identified this way must contain at least two detector fields to be significant on the  $P < 0.05$  level, if the regional *t* value is less than 3.2.

## RESULTS

### *General features*

Table I and fig. 1 show the hemisphere means and the regional distribution in each hemisphere of rCBF measured during rest, automatic speech and humming. Two frontal regions, close to the airways, are excluded in each hemisphere since

TABLE 1. CBF,  $p\text{CO}_2$  AND BP VALUES AT REST, SPEECH AND HUMMING\*

| Measurement conditions | Mean hemisphere grey matter flow<br>( $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ) |                   | $p\text{CO}_2$<br>( $\text{mmHg}$ ) | Mean BP<br>( $\text{mmHg}$ ) |
|------------------------|----------------------------------------------------------------------------------------------------|-------------------|-------------------------------------|------------------------------|
|                        | Right                                                                                              | Left              |                                     |                              |
| Rest (R)               | $78.0 \pm 12.9$                                                                                    | $78.3 \pm 12.5$   | $37.3 \pm 2.1$                      | $112 \pm 15$                 |
| Speech (S)             | $97.7 \pm 14.5$                                                                                    | $96.2 \pm 14.6$   | $38.3 \pm 1.9$                      | $110 \pm 13$                 |
| Humming (H)            | $95.0 \pm 11.2$                                                                                    | $94.3 \pm 11.6$   | $37.7 \pm 2.9$                      | $109 \pm 13$                 |
| S-R                    | $19.7 \pm 13.5^3$                                                                                  | $17.9 \pm 13.8^3$ | $1.0 \pm 1.7^2$                     | $-1.4 \pm 6.3^1$             |
| H-R                    | $17.0 \pm 11.9^3$                                                                                  | $16.0 \pm 12.3^3$ | $0.5 \pm 2.1^1$                     | $-3.3 \pm 8.7^1$             |

\* Mean  $\pm$  SD,  $n = 15$ .  $^1P = \text{n.s.}$ ;  $^2P < 0.05$ ;  $^3P < 0.001$ .

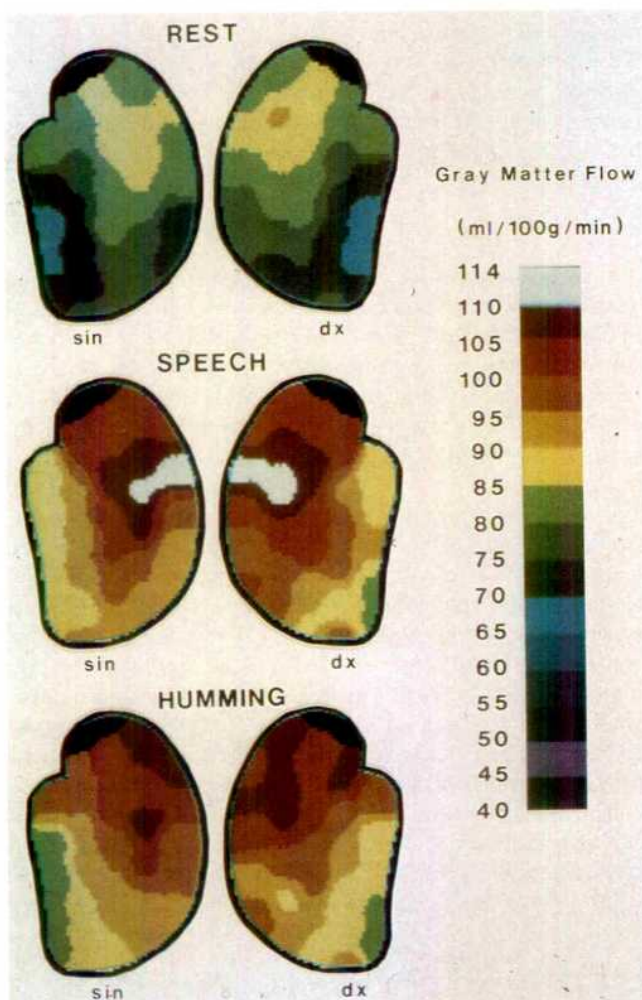


FIG. 1. Regional cerebral blood flow during (top) rest, (middle) speech and (bottom), humming. Mean result in 15 subjects. The rCBF distributions were achieved by linear interpolation between the 28 detector fields over each hemisphere. The hemispheres are seen from the lateral aspect and displayed with the frontal region upwards and the temporal region laterally. Note the high degree of symmetry between the hemispheres both at rest and during activation.

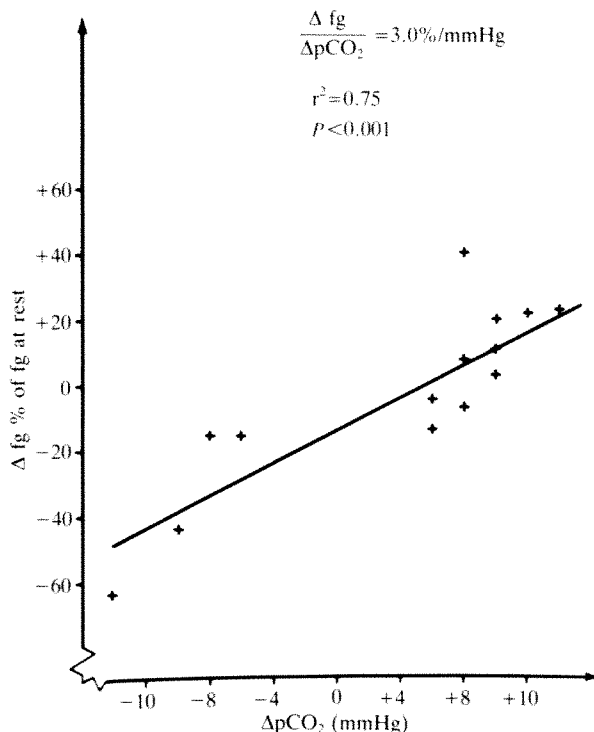


FIG. 2. Relation between CBF, determined as the grey matter flow ( $fg$ ) and changes in  $pCO_2$  produced by inhalation of 6% $CO_2$ /air mixture, in 8 normal subjects and by hyperventilation in 6 normal subjects.

they were not consistently represented in all measurements. There was a highly significant ( $P < 0.001$ ) increase in mean hemisphere CBF from rest for both hemispheres, both for speech and for humming. The increase during speech was more pronounced ( $P < 0.001$ ) on the right than on the left, but there was no such hemisphere difference for humming.

The basic rCBF pattern was highly symmetric in each measurement condition with higher flow levels in frontal regions in both hemispheres. Thus there was a significant correlation between the rCBF patterns for rest, speech and humming ( $r = 0.9$ ,  $P < 0.001$ ) as well as between the hemispheres for each measurement condition ( $r = 0.9$ ,  $P < 0.001$ ).

The average  $pCO_2$  change between the measurement conditions was small ( $< 1.0$  mmHg) and only significant ( $P < 0.05$ ) for speech. However, to avoid  $pCO_2$  changes obscuring the regional CBF changes they were corrected for in the subsequent analysis with a correction factor of 3% per mmHg  $pCO_2$  change from rest (fig. 2) which was obtained from the normal controls.

#### Regional CBF changes

The CBF changes from rest to speech and from rest to humming (fig. 3) showed a significant ( $P < 0.05$ ) interhemisphere linear correlation between the rCBF

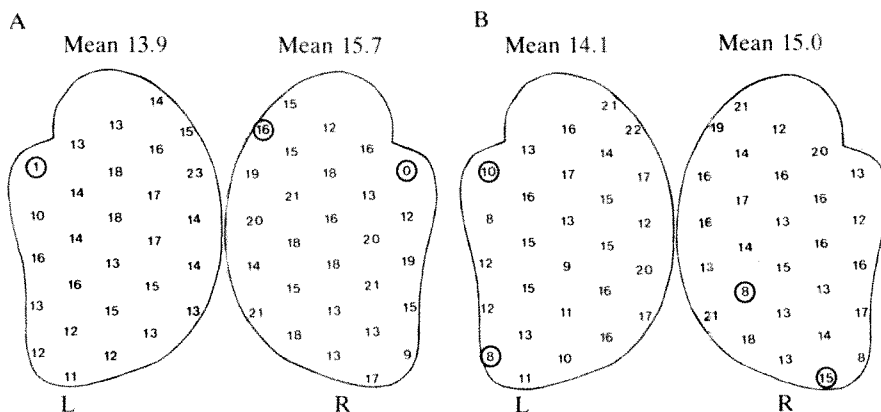


FIG. 3. The rCBF increase from rest during A, automatic speech, and B, humming. The CBF values are corrected for  $p\text{CO}_2$  changes. Mean increases in  $\text{ml}\cdot 100\cdot \text{g}^{-1}\cdot \text{min}^{-1}$  are given for each region. Regions indicated with a circle do not have any significant ( $P < 0.05$ ) rCBF increase during the vocal activations.

changes for corresponding regions in the right and left hemisphere for speech but not for humming. A few regions did not show any significant ( $P < 0.05$ , paired two-tailed t test) rCBF change from rest during speech or humming (fig. 3). Thus there was no global CBF increase, defined as a significant increase in *all* regions, during the activations.

The CBF increase consisted both of regions with a large flow increase in only a few individuals which was absent in others, and of regions with moderate or high flow increase in all subjects. Regions which had a low interindividual variation and which consequently correlated rather to the common activation mode than to an individual activation strategy, were highlighted by division of the rCBF increase by the regional standard error. This is equivalent to a calculation of the regional t statistic (fig. 4). Thus each regional t value represents a significant *focal* CBF increase from rest at  $t \geq 3.0$  (represented by red and white colours in fig. 4) if it contains at least two detector fields or a field with  $t \geq 3.2$ . A strategy in three steps was used to find regions of significant rCBF increase from rest during the activations.

1. 'Preliminary activated regions' (PAR) were identified separately in the speech and humming t maps. The PAR were defined as regions, consisting of one to several adjacent detector fields, where each field had a t value  $\geq 3.0$ .

2. The PAR for speech and for humming were compared and overlapping fields were defined as regions activated both by speech and by humming (fig. 5c).

3. The remaining detector fields in the PAR were then considered to be regions activated only during automatic speech or only during humming. In the final setting of limits for the regions an adjacent detector field was in two cases (fig. 5b, regions 6 and 10) included in the activated regions since its t value (2.8) was clearly more closely related to the activation ( $t \geq 3.0$ ) than to the adjacent region with low ( $< 2.2$ ) t values. Table 2 gives the mean t value  $\pm$  SE of the mean for each activated region.



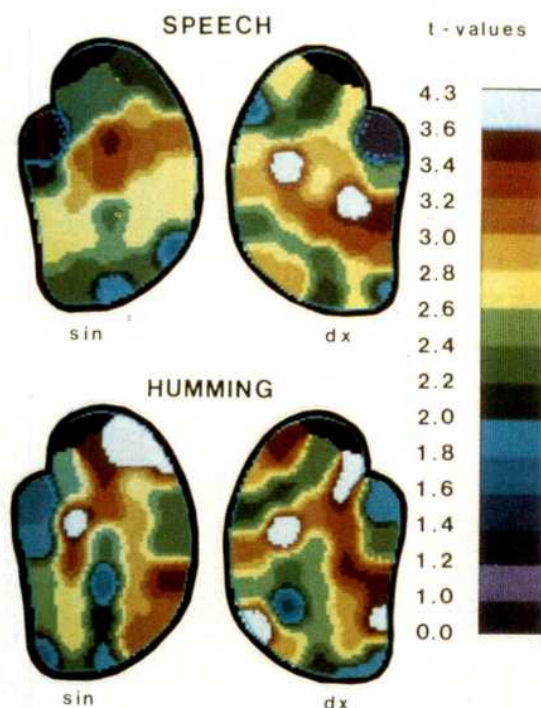


FIG. 4. Regional distribution of CBF increase from rest (corrected for interindividual variations and for  $p\text{CO}_2$  changes), expressed as the regional  $t$  distributions for (top) automatic speech and (bottom), humming. The colour scale gives the  $t$  values. Values above 2.9 indicate regions with significant changes. The  $t$  distributions were achieved by linear interpolation between the 28 detector fields over each hemisphere.

The activated regions in Table 2 are significant on the  $P < 0.05$  level, either for speech or for humming, except region 9 which consists of a single detector field with  $t = 3.0$ .

The regional patterns of  $t$  values at speech and at humming showed both important similarities and differences. The *similarities* included a right posterior temporal region (fig. 5C: region 1), a highly activated region in the right Rolandic area (fig. 5C: region 2) and a left posterior inferior frontal region (fig. 5C: region 3). Both during speech and humming the regions with the lowest  $t$  values (i.e., least changes from rest) were found in the anterior part of the temporal lobes, in the occipital lobes, and for humming also in the inferior part of the parietal and centroparietal areas. The  $t$  value distribution had an equal, but moderate, similarity between the hemispheres for humming and speech ( $r = 0.5$ ,  $P < 0.05$ ).

*Speech* (fig. 5A) gave fewer high  $t$  regions and they were more widespread than during humming. In contrast, the pattern during *humming* (fig. 5B) contained multiple small regions which did not show high  $t$  values during speech, such as in the superior frontal and parietal regions on both sides, and in the inferior frontal region on the right.

TABLE 2. REGIONAL DISTRIBUTION OF *t* VALUES DURING SPEECH AND HUMMING\*

| Region no.                   | 1            | 2   | 3            | 4            | 5            | 6            | 7   | 8            | 9   | 10           | 11           | Remaining<br>detector<br>fields |
|------------------------------|--------------|-----|--------------|--------------|--------------|--------------|-----|--------------|-----|--------------|--------------|---------------------------------|
| No. of<br>detector<br>fields | 3            | 1   | 2            | 4            | 3            | 2            | 1   | 3            | 1   | 4            | 5            | 27                              |
| Speech                       | 3.4<br>± 0.2 | 3.9 | 3.2<br>± 0.2 | 3.1<br>± 0.1 | 3.2<br>± 0.1 | 2.9<br>± 0.1 | 2.8 | 2.7<br>± 0.1 | 2.8 | 2.3<br>± 0.1 | 1.9<br>± 0.1 | 2.2<br>± 0.1                    |
| Humming                      | 3.5<br>± 0.1 | 3.9 | 3.5<br>± 0.2 | 2.6<br>± 0.2 | 2.5<br>± 0.2 | 3.4<br>± 0.6 | 3.2 | 3.3<br>± 0.1 | 3.0 | 3.1<br>± 0.1 | 3.5<br>± 0.2 | 2.2<br>± 0.1                    |

\* Mean ± SEM.

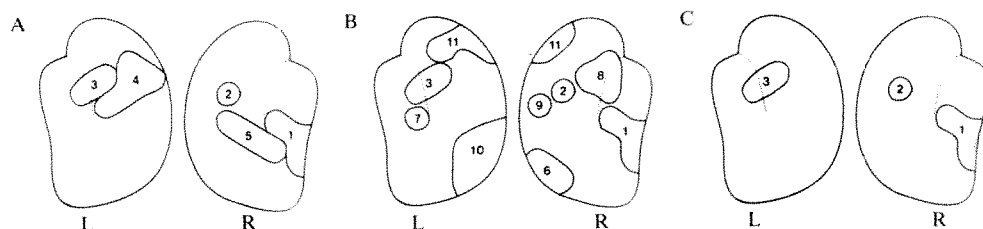


FIG. 5. Regions of significant cortical activation, as indicated by the rCBF increase from rest, during A automatic speech, B, humming, and C, both. The hemispheres are seen from the lateral aspect and displayed with the frontal region upwards and the temporal region laterally. Numbers refer to text (Table 2).

## DISCUSSION

*Technical considerations*

Before discussing the functional substrate of the rCBF changes recorded during speech and humming as shown by the *t* distributions, some general factors influencing rCBF must be considered. It may be argued that the right hemisphere predominance in the recorded rCBF increase during speech and humming in 8 of our patients is due to left hemisphere dysfunction. However, there is nothing in their clinical, CT or EEG findings which indicates that the subjects had any cerebral lesions that could have affected the results at the time of the CBF measurements.

The 3 consecutive rCBF measurements were always made in the same sequence, rest, speech and humming. Consequently, habituation to the rCBF measurement (Risberg *et al.*, 1977), if not counteracted by the activations, would tend to decrease the flow level at the later measurements, which is in contrast to the recorded CBF increase. There was a slight and nonsignificant tendency towards lower blood

pressure during the later rCBF measurements. Small blood pressure changes within the autoregulatory range do not, however, affect the CBF in normals (Olesen, 1973; Strandgaard, 1976). The CBF is sensitive to changes in  $p\text{CO}_2$  (Ackerman *et al.*, 1973; Harper and Glass, 1965), but corrections were made for the small  $p\text{CO}_2$  variations between the measurements.

There was a high degree of interhemisphere symmetry in the regional CBF distribution during rest, speech and humming. This symmetry cannot be explained by a look-through effect between the hemispheres since, due to the rather wide detector collimation, the cerebral cortex immediately beneath the detector has a dominating effect on the rCBF value, and radiation from the contralateral hemisphere influences the CBF approximately equally from all regions in that hemisphere (Bolmsj , 1984). Thus an interhemispheric look-through effect could only have given a slight decrease in the regional CBF resolution. Instead, the inter-hemisphere rCBF symmetry during the vocal activations appeared to be a result of the symmetric rCBF distribution in resting wakefulness (Risberg *et al.*, 1975; Ingvar, 1979; Prohovnik *et al.*, 1980), on which the rCBF increase during speech and humming was superimposed. Thus when the rCBF at rest was subtracted, and the individual variations were corrected for by calculation of 't maps', the distribution of rCBF changes during speech and humming demonstrated important asymmetries (fig. 4).

#### *The speech and humming activations*

The rCBF pattern during automatic speech and humming should be analysed in relation to the performed functions in each case. The automatic *speech* test consisted of a monotonous repetition of a series of well-known words (the names of the weekdays). The pronunciation of these words contains a relatively complex motor performance of the mouth, tongue and larynx with involvement of the corresponding motor and sensory cortical regions. However, the assembly of the motor sequence may be relatively simple since the words are extremely well known, few (7), and the word sequence does not express any meaningful message. The subject listens to his own words and verifies that they are the ones he intends to say, but he does not have to seek any specific message in the word sequence.

*Humming* (with closed mouth and without words) of a simple well-known nursery rhyme contains, in contrast to automatic speech, a simpler sequence of motor activity since the mouth and lips are not activated as much. However, it entails a complex assembly of the motor sequence that is to be performed by the larynx (about 40 tones) and the sequence of tones is intended to convey a specific message (the tune). During humming the subject concentrates on his performance and activates his memory of the tune (possibly also the words), listens to his own voice to verify that the correct sequence of tones is produced, and checks that he conveys an adequate reproduction of the rhythm and emotional content in the tune.

### *Expected findings*

*Speech.* During automatic speech (fig. 5A) activation of rolandic regions in both hemispheres controlling the sensorimotor speech activities would be expected. The distribution of the activated rolandic regions during speech (fig. 5A) was, however, not symmetrically distributed between the hemispheres. While in the left hemisphere there was an extensive activation of precentral (mainly motor) regions, there was, in contrast, in the right hemisphere only activation of the postcentral (sensory) regions, except for one small intensely activated motor region (no. 2). The activation of this small right hemisphere motor region may be due to laryngeal motor activity since humming also gave a similar intense activation. It is interesting to recall that the localization of the region corresponds to the cortical area in which Penfield and Jasper (1954) elicited vocalization on electrical stimulation.

During speech there was also activation of a left inferior posterior frontal region (no. 3) which had a localization that corresponds to Broca's area. This activation was not unexpected, especially if Broca's area is considered to be involved in the assembly of the verbal motor programs executed by the rolandic regions.

*Humming.* During humming (fig. 5B) rolandic activation was limited to the larynx motor region (no. 2) in the right hemisphere. Besides a flow increase in Broca's area on the left, there was also activation of a symmetric area and of an adjacent inferior frontal region (no. 8) in the right hemisphere. This finding is in agreement with Monrad-Krohn's (1947) observation of altered melody of speech in left inferior frontal lesions, presumably involving Broca's area, and with the observation of expressive amusia in right frontal lesions (Botez and Wertheim, 1959). Thus both inferior posterior frontal regions may be involved in the assembly of the motor programs for humming. Broca's area does not, however, appear to be necessary for melody production (Jacome, 1984). The activation of the anterior superior frontal regions (no. 11) in both hemispheres during humming might be related to the subjects' concentration on voice control during humming. Lesions in those frontal regions are known to cause deficiency in focusing and sustaining attention on internal representations (Luria, 1966). This frontal activation may, however, also be related to the theory that the frontal lobes, especially the prefrontal cortex, play a central role in the processing of serial, temporally structured, sequences of information, such as the sequence of tones which gives the melody (Fuster, 1980; Ingvar, 1983, 1985).

Wernicke's area did not show any significant focal activation during automatic speech or humming which presumably was due to the fact that interpretation of meaningful word sequences was not needed during the tests.

### *Other findings*

Both during speech and humming one of the regions most activated was the right posterior temporal region, which in its rostral part includes the right auditory area. Roland *et al.* (1981) found that discriminative listening to tone pairs produced

the largest rCBF increase in this particular region (comprising the right auditory and the inferior temporal regions) as well as in the right midparietal region and the frontal eye fields. These results differ from the findings of Nishizawa *et al.* (1982) who, during listening to simple onomatopoeic words found the dominating rCBF increase to be localized in the left superior temporal region. Rhyme detection and recognition of the word 'tan' in a 'pan-tan' sequence was found by Knopman *et al.* (1982) to give a significant focal CBF increase in the right posterior temporal region. Milner (1962) found that patients with right temporal lobectomy did worse, especially in tests for recognition of timbre and tonal pairs, than those with left temporal lobectomy. Sperry (1966–1967) showed that the right hemisphere can interpret the meaning of concrete nouns. Penfield and Jasper (1954) found that direct stimulation of regions in the temporal lobes could produce a feeling of recognition or dysrecognition. All these findings indicate that the right posterior temporal region may be involved in auditory discrimination, during automatic speech in the recognition of the spoken words, and during humming in the recognition of the melody. Goldenberg *et al.* (1985) found that only the superior parietal regions (mainly the right) showed a significant CBF increase ( $P < 0.05$ , two-tailed, unpaired t test) when listening to meaningless words was compared to listening to abstract nouns. Penfield and Jasper (1954) found that electrical stimulation of the temporal lobes could trigger a temporally structured recall of memory sequences, including hearing of a tune. Heilman *et al.* (1975) found that patients with right hemisphere lesions, mainly parietal, performed significantly worse in a test of the perception of the emotional tone of voice in spoken neutral sentences than patients with similar left hemisphere lesions. The focal CBF increase in the parietal lobes during humming may thus be related to the recall of the memory of the tune (on the right) and the words (on the left) of the hummed nursery rhyme.

### Conclusions

The main results of the present study are apparent in fig. 5.

Cortical activation during *automatic speech* does not exclusively involve the left hemisphere. This confirms the results of Ingvar and Schwartz (1974) and Larsen *et al.* (1978). The present bilateral rCBF measurements in fact indicate that the right hemisphere may 'work' more during automatic speech than the left hemisphere. Furthermore, the findings demonstrate clearly that *humming* of a melody is not exclusively a right hemisphere function. From our results, however, it appears that there may be a high degree of specialization between the hemispheres in the two functions tested.

During *automatic speech*, the *left* hemisphere appears more involved in the preparation of the speech motor programs and in the motor control of the mouth and the tongue since the most pronounced activations were seen in Broca's area and the precentral motor regions. The *right* hemisphere, on the other hand, seems mainly to be involved in laryngeal motor control, as well as in the feed-back

reception and recognition of sensory and auditory information as indicated by the rolandic and temporal activations, respectively.

During *humming*, the *right* hemisphere showed the same (laryngeal?) focus of activation in the rolandic area as well as of the temporal region that appears to be involved in the recognition of auditory information. The bilateral rCBF increase indicates that *both* hemispheres participate approximately equally in the voluntary control, and in the preparation of motor programs for the hummed tune, as well as in memory activation.

The limited resolution of the rCBF system (30 detectors per hemisphere) precludes a more detailed functional analysis or localization of subdivisions of the rather extensive activated cortical regions. However, it appears from the present results that both during automatic speech and humming, numerous functions in both hemispheres cooperate to produce vocal activation. This finding contrasts to classical concepts based originally upon the observations by Broca (1865) and Wernicke (1874) that speech functions are localized exclusively to the left hemisphere. The results are, in fact, in principal agreement with one of the main concepts of Sperry (1968), namely that speech function—and as it seems also musical function—requires the collaboration of both hemispheres in various functional patterns.

#### ACKNOWLEDGEMENTS

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# GENERATOR MECHANISMS OF GIANT SOMATOSENSORY EVOKED POTENTIALS IN CORTICAL REFLEX MYOCLONUS

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## SUMMARY

In order to clarify the generator mechanisms for giant cortical evoked potentials, scalp topographies of somatosensory evoked potentials (SEPs) following various types of stimulation, including electrical nerve trunk and finger stimulation and mechanical stimulation, were investigated in 5 patients with cortical reflex myoclonus. For SEPs evoked by median nerve stimulation, not only the P25 and N34 components in central and parietal regions but also N25 in the frontal region were markedly enlarged in each patient. Their scalp distributions were not significantly different from those of normal subjects. P25 and N25, but not N34, were considerably attenuated by interfering tactile stimulation applied to the hand. The components corresponding to P25, N25 and N34 following electrical stimulation of the digital nerves as well as mechanical stimulation of the finger were also remarkably large and showed scalp distributions similar to those for median nerve SEPs.

It is therefore concluded that the giant cortical SEPs of cortical reflex myoclonus are generated in those areas of the primary sensory cortex which generate normal SEPs, in response to an input, at least in part, from cutaneous afferents on the basis of an extremely enhanced cortical excitability.

## INTRODUCTION

It is well known that, in some myoclonic patients, cortical components of somatosensory evoked potentials (SEPs) are of remarkably high amplitude (Dawson 1946, 1947; Watson and Denny-Brown, 1955; Halliday, 1967; Halliday and Halliday, 1970; Sutton and Mayer, 1974; Chadwick *et al.*, 1977; Shibasaki *et al.*, 1978; Hallett *et al.* 1979; Kelly *et al.*, 1981; Rothwell *et al.*, 1984; Obeso *et al.*, 1985; Shibasaki *et al.*, 1985*b*; Tobimatsu *et al.*, 1985; Cowan *et al.*, 1986) and are often followed by an enhanced long-loop reflex (C reflex, Sutton and Mayer, 1974). These patients usually show premyoclonus cortical spikes if investigated by the jerk-locked averaging method (Shibasaki and Kuroiwa, 1975; Chadwick *et al.*, 1977; Shibasaki *et al.*, 1978, 1985*b*). This type of myoclonus has been called 'pyramidal myoclonus' (Halliday, 1967) or 'cortical reflex myoclonus' (Hallett *et al.*, 1979). Mechanisms generating these 'giant SEPs' have been discussed previously

(Chadwick *et al.*, 1977; Shibasaki *et al.*, 1978; Rothwell *et al.*, 1984; Shibasaki *et al.*, 1985a,b), but the following aspects have not yet been elucidated: (1) the detailed scalp topography of each component; (2) the specific cortical structures responsible for generating such giant potentials; and (3) the identity of the peripheral nerve fibres which are concerned with the generation of the giant potentials.

The present study is therefore aimed at elucidating problems related to the generator mechanisms for the giant SEPs in patients with cortical reflex myoclonus using a variety of methods including conventional electrical stimulation of a nerve trunk, electrical stimulation of digital nerves of the finger using ring electrodes, mechanical stimulation (Kakigi and Shibasaki, 1984) and the interference approach (Jones, 1981; Jones and Power, 1984; Kakigi and Jones, 1985; Kakigi, 1986).

### PATIENTS AND METHODS

Five patients with myoclonus were selected according to the following criteria: (1) the amplitude of the initial cortical positive potential recorded at or around the somatosensory hand area of the scalp following stimulation of the median nerve at the wrist was larger than the mean  $\pm 2$ SD for normal subjects; (2) an enhanced long-loop reflex (C reflex) could be recorded even at rest (without voluntary contraction of the corresponding muscles); and (3) the presence of cortical spikes preceding spontaneous myoclonic jerks using the jerk-locked averaging method (Shibasaki and Kuroiwa, 1975; Shibasaki *et al.*, 1978, 1985b). Patients' profiles are summarized in Table 1. All patients manifested intention as well as postural myoclonus, and they were taking antimyoclonus medication at the usual dose, as listed in Table 1, at the time of study to suppress myoclonus.

TABLE 1. CLINICAL DATA

| Case                            | 1                                                                  | 2                                                               | 3                                             | 4                      | 5                      |
|---------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------|------------------------|------------------------|
| Diagnosis                       | Progressive myoclonic epilepsy                                     | Sialidosis type 2                                               | Sialidosis type 2                             | Uraemic encephalopathy | Uraemic encephalopathy |
| Sex                             | F                                                                  | M                                                               | M                                             | F                      | M                      |
| Age (yrs)                       | 17                                                                 | 55                                                              | 51                                            | 15                     | 62                     |
| Age at onset (yrs)              | 10                                                                 | 26                                                              | 48                                            | 15                     | 62                     |
| Convulsions                     | +                                                                  | +                                                               | +                                             | +                      | -                      |
| Other symptoms                  | Cerebellar ataxia                                                  | Cerebellar ataxia                                               |                                               | Impaired consciousness | Impaired consciousness |
| Medication at the time of study | Clonazepam, 6 mg<br><br>Valproate, 800 mg<br><br>Primidone, 500 mg | Clonazepam, 4 mg<br><br>Valproate, 600 mg<br>Propranolol, 60 mg | Clonazepam, 4.5 mg<br><br>Propranolol, 120 mg | Phenytoin 200 mg       | Clonazepam 3.0 mg      |

Recordings were performed in a quiet room. The patient was seated comfortably in a reclining armchair, encouraged to relax, and was kept awake.

The electrical stimulus was a constant voltage square-wave pulse of 0.2 ms duration delivered to the right median nerve at the wrist. The stimulus intensity was sufficient to produce a definite twitch of the thumb. For recording SEPs in response to finger stimulation, the right middle finger was stimulated using silver ring electrodes with the stimulus intensity approximately 10 mA. For recording SEPs evoked by mechanical stimulation, the dorsum of the middle phalanx of the right middle finger was stimulated by a small plastic ball which was fixed at the tip of a vertically-moving needle. The

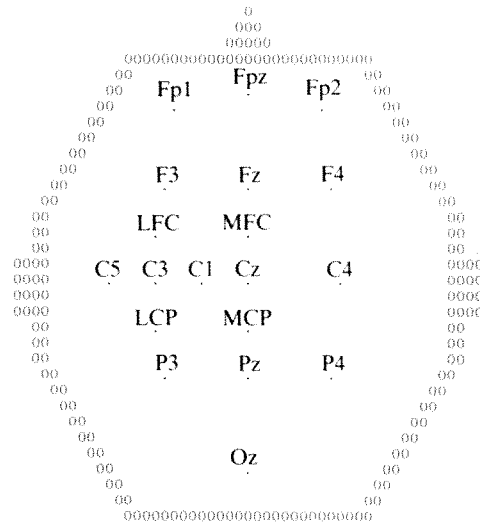


FIG. 1. Electrode placements based on the 10-20 international system. LFC, MFC, LCP and MCP were midway between F3 and C3, Fz and Cz, C3 and P3, and Cz and Pz, respectively. The right earlobe (A2) was used as the reference.

patient felt touch or light pressure when stimulated. The detailed methods were described in our previous paper (Kakigi and Shibasaki, 1984).

In order to establish which kind of peripheral nerve fibres are responsible for generating giant SEPs, interfering tactile stimulation or active finger movement was applied by using the following methods continuously and concurrently with the electrical stimuli to the median nerve. (1) Tactile stimulation. A soft wad of tissue paper was continuously applied by the experimenter to the palm of either hand while the right median nerve was stimulated electrically. (2) Voluntary finger movement. The subject was encouraged to produce a continuous rapid drumming motion with the left fingers while the right median nerve was stimulated electrically. In order to avoid changes in the stimulus conditions, finger movements with the right hand were not performed. For the detailed methods as well as the results in normal subjects, reference should be made to previous papers (Kakigi and Jones, 1985; Kakigi, 1986). Change in amplitude for each component related to interfering stimulation was computed in each case.

Silver disc recording electrodes were attached at 19 scalp locations based on the 10-20 system (fig. 1). LFC, MFC, LCP and MCP electrodes were midway between corresponding sites of the 10-20 system as indicated in fig. 1. The reference electrode was placed on the right earlobe (A2).

The frequency response of the amplifiers was between 1 and 1500 Hz ( $-3$  dB); 500 responses were averaged for median nerve stimulation and 1000 responses for finger and mechanical stimulation. At least three recordings were made for each stimulus condition.

The analysis window was 5–85 ms for the median nerve and mechanical stimulation, and 10–90 ms for electrical stimulation of the middle finger. The sampling rate was 0.16 ms. Responses contaminated with large artefacts over 200  $\mu$ V in amplitude, such as from the electrocardiogram or from muscle activity, were rejected by the computer program.

Peak latency and amplitude were measured for each recognizable component, amplitude being measured from the preceding peak of the opposite polarity. The upper limit of the normal range was the mean  $+2$  SD of the value obtained from normal subjects in our department for each recording session (Table 2). The scalp topography of each consistent component was drawn using two different methods. The first used the peak-to-peak amplitude of each peak identified visually by the experimenter at each electrode to show its scalp distribution. The second, the 'isopotential' map, was

drawn using the amplitude from baseline at each electrode at a particular time interval after stimulus onset. The baseline was determined by averaging the first 10 ms of the analysis window at each electrode. Relative positivity at grid 1 resulted in a downward deflection in all recordings. Each recognizable component was named on the basis of the similarity of its waveform to that of the normal SEPs, as in our previous reports (Kakigi and Shibasaki, 1984; Kakigi, 1986), and it was based on the polarity and peak latency.

## RESULTS

### *SEPs following stimulation of the median nerve at the wrist*

As the waveforms of the early peaks were similar to those in normal subjects except for amplitude, the nomenclature used for the normal data reported by Kakigi (1986) was adopted, as shown in fig 2. N19, P25 and N34 at the LCP electrode correspond to N20, P25 and N33 reported in the previous paper on myoclonus, respectively (Shibasaki *et al.*, 1978, 1985*b*). Their peak latencies were within the normal range in each patient except for Case 5 in which they were slightly prolonged. The amplitude of N19 (range 3.8–6.0  $\mu$ V) was within the normal range in Cases 1 and 3, at the upper limit in Case 2, and slightly increased in Cases

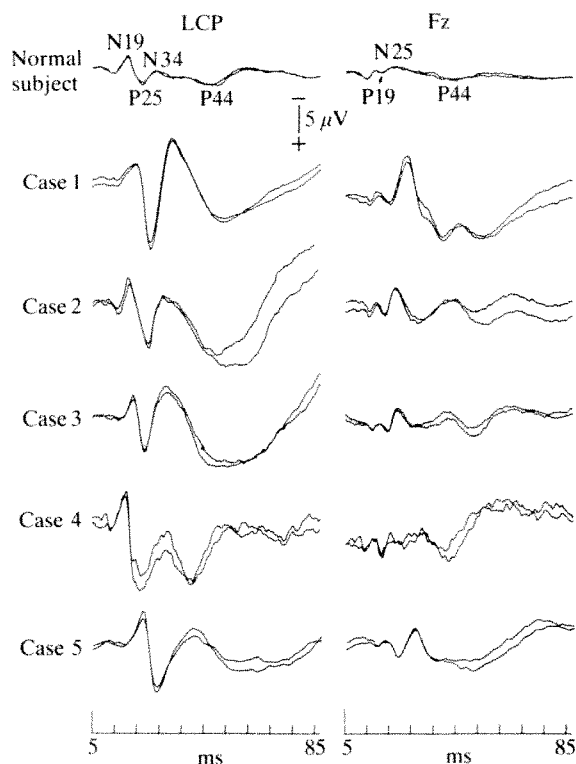


FIG. 2. Waveforms of SEPs following stimulation of the right median nerve at the wrist at 2 selected electrodes in a normal subject to show the nomenclature of each recognizable peak and in all 5 cases.

TABLE 2. AMPLITUDE OF RECOGNIZABLE COMPONENTS IN NORMAL SUBJECTS AND IN PATIENTS WITH CORTICAL REFLEX MYOCLONUS

| Stimulus condition        | Electrode | Component | Amplitude ( $\mu V$ ) |          |        |
|---------------------------|-----------|-----------|-----------------------|----------|--------|
|                           |           |           | Normals               | Patients |        |
|                           |           |           |                       | Range    | (Mean) |
| Median nerve, electrical  | LCP       | N19       | $3.0 \pm 1.2$         | 3.8– 6.0 | (4.8)  |
|                           | Fz        | P19       | $1.0 \pm 0.5$         | 1.5– 3.0 | (2.3)  |
|                           | LCP       | P25       | $4.2 \pm 2.2$         | 9.2–15.0 | (12.4) |
|                           | Fz        | N25       | $1.6 \pm 0.8$         | 3.1– 7.6 | (4.9)  |
|                           | LCP       | N34       | $3.4 \pm 2.0$         | 7.0–17.0 | (10.8) |
| Middle finger, electrical | LCP       | N19       | $0.9 \pm 0.5$         | 0.8– 2.1 | (1.4)  |
|                           | Fz        | P19       | $0.3 \pm 0.2$         | 0.2– 1.0 | (0.7)  |
|                           | LCP       | P25       | $0.9 \pm 0.7$         | 2.8– 7.2 | (4.2)  |
|                           | Fz        | N25       | $0.7 \pm 0.3$         | 1.8– 5.1 | (2.9)  |
|                           | LCP       | N34       | $1.2 \pm 0.8$         | 3.6– 6.3 | (4.7)  |
| Middle finger, mechanical | LCP       | N24(M)    | $0.1 \pm 0.1$         | 0.2– 0.7 | (0.3)  |
|                           | Fz        | P25(M)    | $0.1 \pm 0.1$         | 0.2– 1.0 | (0.4)  |
|                           | LCP       | P29(M)    | $0.2 \pm 0.2$         | 1.0– 1.8 | (1.4)  |
|                           | Fz        | N30(M)    | $0.3 \pm 0.2$         | 0.8– 1.4 | (1.1)  |
|                           | LCP       | N36(M)    | $0.3 \pm 0.3$         | 1.5– 2.4 | (2.0)  |

4 and 5 (Table 2). The amplitude of P25 ranged from 9.2 to 15.0  $\mu V$  (normal  $4.2 \pm 2.2$ ), and that of N34 from 7.0 to 17.0  $\mu V$  (normal  $3.4 \pm 2.0$ ) (Table 2).

For the early cortical components recorded at the frontal electrodes, P19 and N25, their peak latencies at the Fz or F4 electrode,  $20.4 \pm 2.0$  ms (range 18.0–23.0) and  $24.8 \pm 2.5$  ms (23.2–28.0), respectively, showed no significant difference from those of N19 and P25 at the LCP or P3 electrode,  $19.9 \pm 1.9$  ms (17.8–23.0) and  $25.1 \pm 2.6$  ms (23.2–29.0), respectively (paired *t* test). Clear potentials could also be identified in the central and parietal regions ipsilateral to the stimulated nerve (*see* the waveforms recorded at C4 and P4 in fig. 3). The waveforms at those electrodes were very similar to those recorded at the frontal electrodes.

Scalp topographies of P25, N25 and N34 in each case, as well as in a normal subject whose data were selected as being typical in terms of the waveforms and the scalp topographies, are shown in figs 4A and 5A, respectively. The isopotential maps at the latency when the amplitude of P25 and N34 as measured from the baseline was maximal are shown in figs 4B and 5B, respectively. For comparison of scalp topographies between normal subjects and the present cases, three parameters were adopted as follows: (1) the maximal point of each component, (2) the distribution of each component, and (3) the orientation of as well as the bordering area between their scalp distributions. P25 was maximal at the LCP electrode in 4 cases and at the C3 in 1 (Case 1). It spread to the surrounding area as far as the Pz or P4 electrode. N25 was maximal at the Fz or MFC electrode, and was recorded over the frontal region bilaterally and over the central region ipsilateral to the stimulated nerve. Although the waveform recorded at the F3 electrode appeared to be an independent one or a composite of the frontal and the parietal potentials

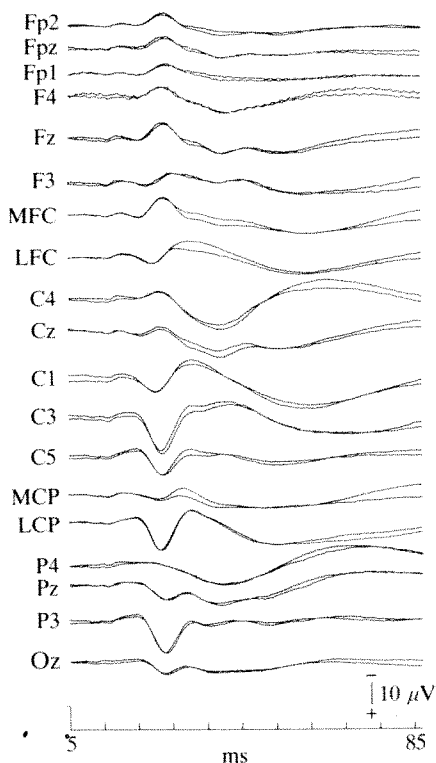


FIG. 3. Waveforms of SEPs at all electrodes studied, following stimulation of the right median nerve at the wrist in Case 1.

in 2 out of 5 cases (*see* waveform at the F3 electrode in fig. 3), we considered its main component to be the negative peak as in 3 other cases in the present study. The two scalp distributions were bordered on a line connecting the LFC and Cz or MCP electrodes (figs 4A, B).

The scalp topography of the P25-N25 complex in the present cases was not significantly different from that of our normal subjects or from the topographies reported previously (Desmedt and Bourguet, 1985; Tsuji and Murai, 1986), in terms of the 3 parameters described above. The scalp topography of the N19-P19 complex was very similar to that of the P25-N25 complex, although it was not shown in the figure. The following component, N34, was maximal at the C3 electrode in 3 cases and at the LCP electrode in 2 cases (fig. 5). It spread to the frontal and the central region as far as the F3 and the Cz electrodes, respectively. The scalp topographies of N34 in the present cases were not significantly different from those in normal subjects. They were similar to those of P25 in the present cases, but N34 was maximal more anteriorly than P25 (*see* figs 4A, 5A). As N34 did not exceed the baseline in Cases 2 and 4, or in the normal subject, (fig. 2), the isopotential maps at the latency when N34 was maximal in those cases looked different from those in 3 other cases in which N34 was very large and clearly

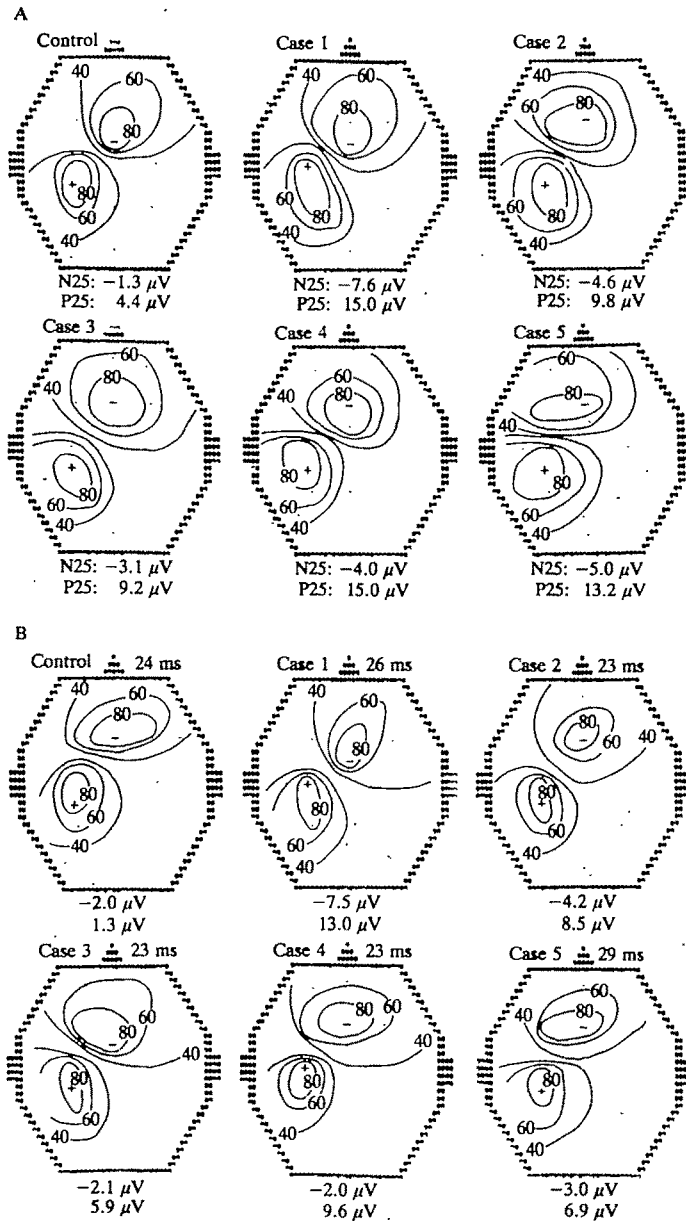


FIG. 4. Scalp topography of P25-N25 complex in a normal subject as well as in each individual case. In A, it was drawn using the peak-to-peak amplitude to show the distribution of P25 and N25, and in B, it was drawn using the amplitude from the baseline at the latency when P25 was maximal in each individual record (isopotential maps). Electrodes marked - or + show the maximal point of each negative or positive component, respectively, and its amplitude is shown below each figure. 80, 60, 40 are the percentage amplitudes with respect to the maximal point.

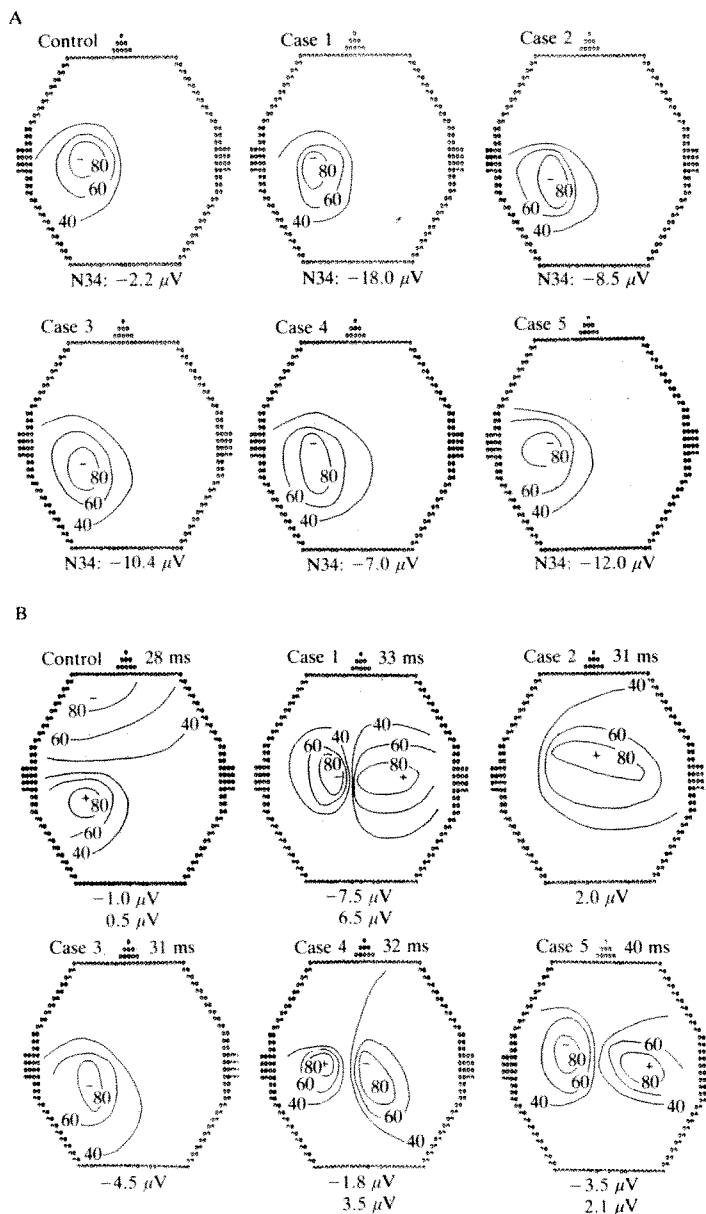


FIG. 5. Scalp topography of N34 component based on the peak-to-peak amplitude (A), and isopotential maps at the latency when N34 was maximal in each individual record (B) (see legend for fig. 4).

exceeded the baseline (fig. 5B). The amplitude of N34 in Table 2 was slightly different from that shown below each map in fig. 5A in Cases 1, 4 and 5, because, in Table 2, the amplitude measured at the LCP electrode was shown in every case, whereas in fig. 5A, that at the maximal point (C3 in those 3 cases) was shown.



*Interference effects*

Interference effects at 2 selected electrodes, LCP and Fz, are shown in Table 3 and fig. 6. Continuous tactile stimulation applied to the palm ipsilateral to the stimulated nerve markedly reduced the amplitude of N19 at the LCP electrode as well as that of P19 at the Fz electrode in every case. P25 at the LCP electrode as well as N25 at the Fz electrode were markedly reduced in all cases except for Case 3 in whom reduction was slight. These changes were relatively larger compared with those in normal subjects (Table 3). N34 at the LCP electrode was moderately

TABLE 3. PERCENTAGE CHANGE IN AMPLITUDE OF SEP<sub>s</sub> FOLLOWING STIMULATION OF THE MEDIAN NERVE AT WRIST RELATED TO CONCURRENT INTERFERING STIMULATION

|                                             |           |           |          | Case |     |     |     |     |
|---------------------------------------------|-----------|-----------|----------|------|-----|-----|-----|-----|
|                                             | Electrode | Component | Control* | 1    | 2   | 3   | 4   | 5   |
| Tactile stimulation,<br>ipsilateral palm    | LCP       | N19       | -29      | -41  | -29 | -36 | -34 | -21 |
|                                             | Fz        | P19       | -34      | -69  | -28 | -76 | -39 | -36 |
|                                             | LCP       | P25       | -30      | -48  | -25 | -4  | -40 | -62 |
|                                             | Fz        | N25       | -33      | -60  | -57 | -10 | -13 | -59 |
|                                             | LCP       | N34       | 42       | -39  | 0   | -16 | 88  | -10 |
|                                             | LCP       | P44       | -23      | -4   | 62  | -33 | 80  | 21  |
| Tactile stimulation,<br>contralateral palm  | LCP       | N19       | 2        | -1   | -6  | -24 | -3  | 7   |
|                                             | Fz        | P19       | 3        | 41   | 0   | 32  | 0   | -5  |
|                                             | LCP       | P25       | -3       | -2   | 17  | -12 | -11 | -5  |
|                                             | Fz        | N25       | 12       | 13   | -12 | 41  | 20  | 25  |
|                                             | LCP       | N34       | -2       | 5    | -5  | -13 | 87  | -3  |
|                                             | LCP       | P44       | 9        | 40   | 22  | 0   | 91  | 61  |
| Voluntary movement,**<br>contralateral hand | LCP       | N19       | -3       | 4    | 72  | 13  | —   | —   |
|                                             | Fz        | P19       | -5       | 10   | 0   | -9  | —   | —   |
|                                             | LCP       | P25       | -14      | 13   | 10  | -39 | —   | —   |
|                                             | Fz        | N25       | -16      | 4    | -21 | -18 | —   | —   |
|                                             | LCP       | N34       | -22      | 0    | -1  | -24 | —   | —   |
|                                             | LCP       | P44       | -18      | -24  | -15 | 17  | —   | —   |

\*The average change in 15 normal subjects.

\*\*This task could not be performed in Cases 4 and 5 because of impaired consciousness.

reduced in Case 1, was not significantly changed in Cases 2, 3 and 5, and was markedly enhanced in Case 4. N34 was usually enhanced in normal subjects (Table 3). This difference appeared to be related to the remarkable reduction of the preceding P25 in the present cases (fig. 6).

Continuous tactile stimulation of the contralateral hand caused no consistent change in any of the recognizable component (Table 3). Voluntary movements of the fingers contralateral to the stimulated nerve showed no apparent effect except in Case 3 in which P25 and N34 at the LCP electrode were moderately reduced (Table 3).

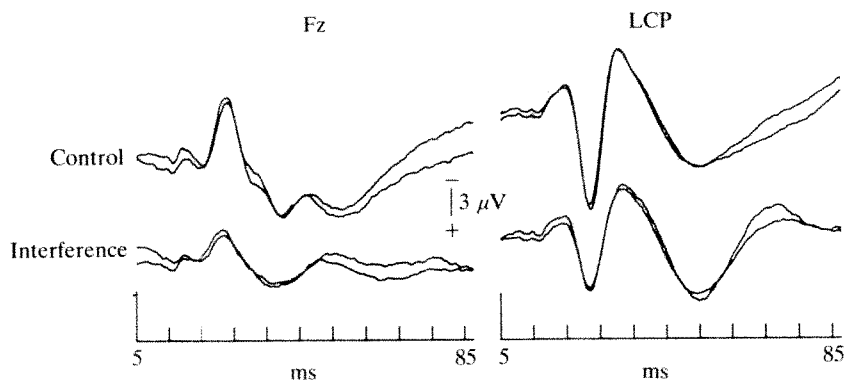


FIG. 6. Waveform changes of SEPs at 2 selected electrodes following stimulation of the right median nerve at the wrist by concurrent tactile stimulation applied to the right palm. The *upper* trace shows conventional SEPs (Control) and the *lower* SEPs with interference (Interference).

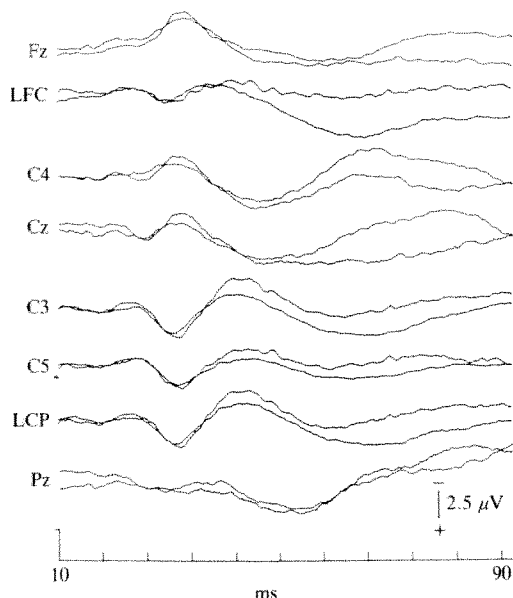


FIG. 7. Waveforms of SEPs at 8 selected electrodes following stimulation of the right middle finger in *Case 1*.

#### *SEPs following stimulation of the right middle finger*

The waveforms (fig. 7) were almost the same as those of the normal subjects (Kakigi and Shibasaki, 1984) as well as those following median nerve stimulation in the present study. The amplitude of the components corresponding to N19 and P19 was within the normal range (Table 2). However, the amplitude of the following components corresponding to P25, N25 and N34 was above the normal range in every case, approximately 4 to 5 times as large as the average amplitude in normal subjects (Table 2). Scalp distributions of these potentials showed no significant difference as compared with those of P25–N25 and N34 of the median nerve SEPs (see figs 4, 5).

### Mechanical stimulation

Consistent waveforms (fig. 8) were identified following mechanical (touch) stimulation of the right middle finger in each subject, although they were not so clearly recognized as with the electrical stimulation SEPs. As for the electrical stimulation SEPs, the amplitude of N24(M) and P25(M), which corresponded to N19 and P19, respectively, was above the normal range in Case 2, but was within the normal range in other cases (Table 2). In contrast, the amplitude of P29(M), N30(M) and N36(M) was much larger than the normal range in every case, about 7 times as large as the average amplitude of normal subjects. Scalp distributions of those potentials were similar to those of the corresponding components of the median nerve SEPs, although the components following mechanical stimulation were more restricted in each region.

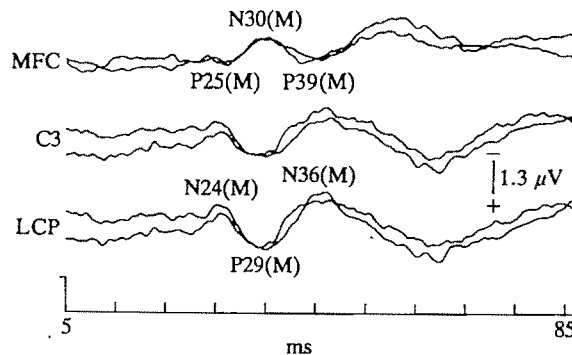


FIG. 8. Waveforms of SEPs at 3 selected electrodes following mechanical (M) stimulation of the right middle finger in Case 2.

### DISCUSSION

The first report describing giant SEPs in patients with myoclonus dates back to 1946, when Dawson found unusually large SEPs, maximal over the precentral area, in patients with progressive myoclonic epilepsy. Since then it has been well established that giant SEPs can be recorded in 'pyramidal myoclonus' (Halliday, 1967) or 'cortical reflex myoclonus' (Hallett *et al.*, 1979). However, there has been no detailed study of scalp topography of SEPs following various kinds of stimulation in cortical reflex myoclonus.

For the SEPs that follow stimulation of the median nerve at the wrist, the waveform and scalp distributions of the early cortical potentials in all 5 cases of the present study were very similar to those in normal subjects, although their amplitude was extremely large except for N19 and P19. The amplitude of N19 and P19 was within or slightly larger than the normal range, as in our previous report (Shibasaki *et al.*, 1985b). These peaks should be considered to be cortical rather than the subcortical potentials, since they showed a clearly localized distribution. If giant potentials in cortical reflex myoclonus represent postsynaptic hyper-

excitability of the cortex, as we have discussed previously (Shibasaki *et al.*, 1985b), N19 and P19 can best be explained as presynaptic activity originating from the primary sensory cortex, probably area 3b (see Jones and Power, 1984; Kakigi and Jones, 1985; Kakigi, 1986). Jones (1982) reported a patient with progressive myoclonic epilepsy whose N19 was very large. Although that patient may represent a very rare case, cortical reflex myoclonus could have a variety of different physiological mechanisms in terms of excitability of the central nervous system.

As reported in previous papers (Halliday, 1967; Shibasaki and Kuroiwa, 1975; Shibasaki *et al.*, 1978; Rothwell *et al.*, 1983; Obeso *et al.*, 1985; Shibasaki *et al.*, 1985b), the P25 potential was unusually large in all 5 cases in the present study. It was maximal at the centroparietal or parietal electrodes contralateral to the stimulated nerve, and was localized around the central and parietal regions. The N25 potential recorded at the frontal electrodes was also very large, being maximal around Fz, and showed an apparent polarity reversal against P25 across the contralateral central electrodes (fig. 4). As it is difficult to consider that the frontal cortex is bilaterally hyperexcitable like the contralateral primary sensorimotor cortex, it seems reasonable to consider that the frontal potential, N25, is due to the orientation of dipolar activities generated in the contralateral sensorimotor cortex.

P25 and N25 were considerably reduced by tactile interference applied to the palm ipsilateral to the stimulated nerve in 4 out of 5 cases (Table 3). The components following electrical stimulation and mechanical tactile stimulation of the middle finger, which correspond to P25 and N25 of the median nerve SEPs, were also very large, and showed similar scalp distributions to those of P25 and N25. Moreover, the magnitude of amplitude enhancement in those two stimulus conditions, approximately 4 to 5 times and 7 times as large as the average amplitude of normal subjects, respectively, was larger than that following median nerve stimulation (about 3 times) (Table 3). These findings could suggest that cutaneous fibres, which were related to tactile stimulation, contribute, at least in part, to the generation of the giant P25 and N25, although some contribution by muscle afferents cannot be totally excluded. Area 3b in the primary sensory cortex is mainly responsive to the input from cutaneous fibres (see Kaas *et al.*, 1981). As it is situated on the posterior bank of the central sulcus, the direction of the dipole generated there should be anteroposterior. The most likely generator of the giant P25 and N25 in cortical reflex myoclonus is therefore considered to be area 3b.

However, if only a horizontal dipole in area 3b was to generate the giant P25–N25 complex, P25 recorded at the C3 electrode, which is supposed to lie just over the hand region of the primary sensorimotor cortex, is expected to be absent or much smaller than that at the parietal electrodes. In addition, the amplitude of P25 and N25 still remained relatively large even when the interference was applied, although they were considerably reduced. There might therefore be a possibility that other regions such as areas 1, 2, 3a or 4, or the association sensory cortex, could also partially contribute to the generation of the giant P25 and N25 potentials

as suggested by Lueders *et al.* (1983), Kakigi (1986) or Tsuji and Murai (1986), based on the study of normal subjects.

Unlike the giant P25–N25 complex, the N34 component was not enlarged in 2 out of our 5 cases, in which it did not exceed the baseline, probably because of a preceding extremely large positive deflection, P25 (fig. 2). This discrepancy was not related to the aetiology of the disease, since N34 was small in 1 of the 2 cases with sialidosis type 2 and in 1 out of the 2 cases with uraemic encephalopathy. In addition, the interference effects on N34 was not consistent among cases (Table 3). The generator mechanism of the giant N34 could therefore be different from that of the giant P25–N25 complex. N34 was maximal more anteriorly around the C3 electrode, compared with the preceding P25 potential. Moreover, it was more clearly identified in the isopotential maps, as in Cases 1 and 5 in fig. 5B, in which the negative deflection spread to the frontal region as far as F3 electrode. Thus it seems reasonable to consider the generator source of the giant N34 to be in the more anterior regions compared with that of the giant P25, probably area 3a or motor cortex. The amplitude difference of N34 from case to case might reflect the variable excitability of the precentral area at the time of recording, although the enhanced C reflex and prejerck spike were identified in every case.

Waveforms recorded in the central region over the ipsilateral hemisphere, that is, those at the C4 electrode, were very similar to those observed in the frontal region in all 5 cases. The amplitude of such ipsilateral potentials become gradually smaller with increasing distance away from the frontal electrodes. It therefore seems reasonable to consider that the ipsilateral central potentials could be due to volume-conducted activities from the frontal region.

The peak latencies of the short and middle-latency potentials, N19, P19, P25 and N25, were within or slightly greater than the normal range in the present study. Mervaala *et al.* (1984) reported that the peak latencies of those potentials were significantly prolonged in 16 patients with progressive myoclonic epilepsy. The difference between their results and ours could be due to the difference in the cause and severity of the disease, since the latencies were not as prolonged in the mildly affected cases of Mervaala *et al.* (1984).

In conclusion, generating mechanisms of giant SEPs in cortical reflex myoclonus appear to involve an extremely enhanced excitability in particular areas of the primary sensory cortex which generate normal SEPs. As the C reflex was enhanced and a premyoclonus spike was identified by the jerk-locked averaging method in every case, it was conceivable that motor cortex could be also hyperexcitable in patients with cortical reflex myoclonus. Recently, Lee *et al.* (1986) recorded a cortical potential preceding voluntary muscle contraction clearly over the post-central region using electrodes placed in the subdural space over the brain in intractable epileptic patients. In primates, pyramidal tract cortical neurons were identified not only in the motor cortex but also in primary sensory cortex (Soso and Fetz, 1980; Murray and Coulter, 1981; Fromm and Evarts, 1982). These findings appear to support the present results and might indicate the possibility

that the postcentral cortex contributes to the generation not only of giant SEPs but also, in part, to an enhanced C reflex and premyoclonus spike, although the pyramidal tract projection from the postcentral cortex to the motoneurons of the anterior horn of the spinal cord might not be as strong.

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# A NEW LOOK AT THE HUMAN SPLIT BRAIN

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## SUMMARY

The 'split-brain' syndrome results from the severance of neocortical commissures, and it is characterized by an incapacity of the cerebral hemispheres to exchange information and by the coexistence of two independent cognitive systems in the same cranium. Research on commissurotomy patients, for the most part, has focused on the disconnection and has treated the hemispheres as two independent entities. A different perspective was adopted in the present study, which considered the 'split brain' as a single organism, and the two disconnected hemispheres as integral components of this organism connected to one another through subcortical structures. Eight independent tasks were conducted on 2 commissurotomy patients who were presented tachistoscopically with simultaneous bilateral information such that neither hemisphere received sufficient information to make a final decision. Only by combining the initially segregated information could a correct response be produced. Both patients performed significantly above chance in 7 of the tasks (spatial orientation, calculation, lexical decision), suggesting that the information divided between the hemispheres could be united, related, and acted upon in a unified manner. This performance was achieved in spite of each hemisphere being unaware of the information received by the other, as typically observed in 'split-brain' patients. The results indicate the coexistence of perceptual disunity and behavioural unity, and they suggest that, even when the two disconnected hemispheres receive different information, the commissurotomy brain works as a single and unified organism.

## INTRODUCTION

Section of forebrain commissures has resulted in a dramatic disconnection syndrome characterized by the coexistence of two independent cognitive systems within the same brain. In laboratory situations where the input can be directed to only one hemisphere, commissurotomy patients typically behave as if they had 'two separate conscious entities or minds running in parallel in the same cranium, each with its own sensations, perceptions, cognitive processes, learning experiences, memories and so on' (Sperry, 1966–1967 p. 318). A large body of empirical findings has accumulated in support of this view, indicating that the forebrain commissures are necessary to join the neural events of each hemisphere into experiential unity.

Although the demonstration of the callosal disconnection syndrome is based on robust evidence (Bogen, 1985), there are theoretical and empirical arguments suggesting that the two disconnected hemispheres are not strictly independent, and



that the commissurotomy does not prevent all communication and relationship between the two sides of the brain. That emphasis has been put above all on the disconnection is illustrated by the label 'split-brain', coined to qualify these patients and which may be somewhat of a misnomer since only fibres linking the two cortices are severed, whereas subcortical brain structures remain undivided and provide a common stem to the two cerebral hemispheres. This is more than a question of semantics and reflects a conceptual orientation that has proven powerful in determining the position of the problem, the experimental approach, and the interpretation of the data. Specifically, this orientation has led investigators to consider the two sides of the brain as being independent and to design experiments that encouraged the two hemispheres to operate in isolation from each other, right through from stimulus reception to response production. Thus in typical experiments on commissurotomed patients, each hemisphere is stimulated separately and has to respond as a function of the information it receives, and the outcome generally confirms the hypothesis of hemisphere independence. This may not entirely qualify as a demonstration of separate processing because the experimental design inherently implies such independence.

Interest in interhemispheric communication is now growing, and subcortical transmission has been inferred from the results of several visual experiments in which performance of one hemisphere is assessed as a function of the information received by the other. Thus commissurotomed patients report verbally the presence and direction of large moving stimuli appearing for a long duration in the left visual field which projects to the mute right hemisphere (Trevarthen and Sperry, 1973), suggesting that the left hemisphere, which has exclusive control over speech production mechanisms, has access to some of the information received by the right hemisphere. Subcortical interhemispheric transfer can also mediate the orientation of attention across the entire visual field (Holtzman *et al.*, 1981; Holtzman, 1984), and Myers and Sperry (1985) reported that commissurotomed patients have the capacity to provide some left-hemisphere generated verbal connotative information about a stimulus projected to the right hemisphere. This interhemispheric transfer is nonetheless quite crude and slow compared with that observed in intact subjects (Sergent and Myers, 1985). Myers and Sperry (1985) summarized the evidence by pointing out that 'subcortical transmissions are largely connotative, contextual, or orientational in nature', and that each hemisphere remains essentially unaware of most of the information received by the other. It is thus believed that subcortical interhemispheric transfer does not override the disconnection syndrome and cannot mediate the exchange of information that would be required for experiential unity: only forebrain commissures allow the brain to operate as a single organism.

Yet despite having two independent cognitive processors, commissurotomed patients seldom display signs of confusion and dissociation in their activities outside the laboratory. They behave as unified individuals and their two hemispheres seem to be able to aim at the same goal. One explanation that has been proposed is that

the same information is projected to both hemispheres through head and eye movements, and therefore that the two hemispheres share the same experience. Such an explanation may not be sufficient, however, because the two hemispheres have been shown to reach different decisions after processing the same information (Levy and Trevarthen, 1976). Some mechanisms must therefore be involved in resolving potential conflict between the outcome of the operations separately performed by each hemisphere. Another explanation has invoked a process of 'metaccontrol' (Levy and Trevarthen, 1976), whereby one hemisphere would be, so to speak, shut off and would not register and process information. Behaviour would thus be under the exclusive control of only one hemisphere and free of any potential interhemispheric conflict. This explanation is not supported by empirical evidence, which shows that the two disconnected hemispheres can simultaneously attend to, and process, the information each receives, with no indication of perceptual erasure in one hemisphere or the other (Sergent, 1983).

No valid explanation is therefore left to account for the absence of disconnection and the mental unity displayed by commissurotomed patients in their day-to-day activities, and only recently has this aspect of their behaviour been investigated experimentally. MacKay and MacKay (1982) examined symbolic information exchange between the two hemispheres of a callosotomized patient and found no evidence of diverging or independent normative hemisphere systems. Sergent (1986) presented the two hemispheres of commissurotomed patients with information associated with opposite responses, and observed that the two disconnected hemispheres were able to cooperate in resolving the conflict. These two findings may then indicate that subcortical structures do not simply serve as pathways linking the two hemispheres but contribute to the orientation and coordination of hemisphere processing as a function of a common goal. However, the empirical evidence reported by MacKay and MacKay (1982) and Sergent (1986) is not unequivocal and suffers from at least two weaknesses. For one, this evidence is only indirect and relies on negative findings of absence of conflict or divergence between the two hemispheres but not on a demonstrated presence of cooperation. For another, the two hemispheres are still treated as single entities, and at least one hemisphere received the entire information required to make a correct response, which leaves the possibility that this hemisphere could trigger the response irrespective of the information received by the other, and thus without need for transfer or cross-integration of hemisphere information.

The foregoing considerations illustrate some of the paradoxes and complexities inherent in the evaluation of the functioning of the so called 'split brain'. While empirical evidence points to mental disunity at the level of information *content* (sensations, percepts, memories), observations of commissurotomed patients outside the laboratory reveal unity and coherence of *behaviour*. Different operational criteria therefore lead to different conclusions about mental unity in these patients, and it has then to be determined whether unity of action and integrated behaviour can be achieved despite disunified consciousness at the level of content

of hemisphere information. The approach adopted here to address this question considers the commissurotomed brain as a single organism in a single cranium, and the cerebral hemispheres as integral components of this organism, connected to each other through subcortical structures.

The purpose of the present study is therefore to seek direct and unequivocal positive evidence that the two disconnected hemispheres are capable of coordinating their activity and integrating the outcome of their respective operations. Two commissurotomed patients were presented with 8 different tasks so designed that the two disconnected hemispheres were simultaneously stimulated with information, the combination of which was the *sine qua non* for the production of a correct response. Neither hemisphere was provided with sufficient information to make a final decision on its own, and only by combining the initially segregated information could the patients produce an accurate response. The current understanding of the callosal disconnection syndrome would typically predict an inherent incapacity of the patients to perform these tasks, but the view that subcortical structures mediate the coordination of hemisphere activity (Sergent, 1986) would suggest that such an integration is within the functional capacity of the commissurotomed brain.

## EXPERIMENT

All the tasks were constructed on the same basic design. They involved bilateral simultaneous tachistoscopic presentation of visual information and a manual-timed response that could be initiated by either hemisphere and that compelled the patients to make a quick decision, without being given the time necessary to resort to cross-cueing strategies. Each task was carried out independently, in the order reported.

### *General method*

#### *Subjects*

The subjects were 2 commissurotomed patients, a 53-year-old woman (N.G.) and a 34-yr-old man (L.B.), who had undergone section of the corpus callosum and of the anterior, hippocampal and habenular commissures (as well as a large massa intermedia in N.G. and the right fornix in L.B.), in 1963 and 1965, respectively. They have been tested extensively since their operation and have displayed the typical disconnection syndrome (Bogen, 1985). Details of their surgical and neurological history have been reported repeatedly (Bogen and Vogel, 1975; Sergent, 1986). They are both under anticonvulsant medication and, while N.G. has had no definite seizures since 1972, L.B. still has minor attacks during sleep or on waking.

Recent investigation by magnetic resonance imaging (MRI) has confirmed a complete section of forebrain commissures in N.G. (Bogen *et al.*, 1986). The radiologist's report on MRI scans of L.B.'s brain also indicates complete section of forebrain commissures, but a small patch of filmy substances is detectable in the centre of the splenium of the corpus callosum. This is not thought to reflect spared callosal fibres, especially given the location of the patch, and further scans with higher resolution are planned to verify this (J.E. Bogen, personal communication).

*Equipment and stimuli*

The stimuli were presented via a Gerbrands tachistoscope and were rear-projected on a translucent screen located 57 cm from the subject's eyes. A response panel containing a central knob and 2 lateral Morse keys was placed in front of the subject. The Morse keys were located 17 cm on each side of the central knob. The subject rested the middle finger of the responding hand on the knob and moved this hand toward 1 of the 2 keys to make a response. Stimulus onset triggered an electronic timer (Gerbrands, model 130) which was stopped when the subject pressed 1 of the 2 keys. Both speed and accuracy of responses were recorded.

In Tasks 1 to 7, the stimuli appeared as white ( $242 \text{ cd/m}^2$ ) on a dark background ( $4.2 \text{ cd/m}^2$ ), as illustrated in fig. 1, and the experiments were conducted in a dimly lit room. Except in Task 7, the inner edge of each lateral stimulus was located  $2.5^\circ$  from fixation. The spreading of light from the stimulus was less than  $2^\circ$  of visual angle and did not extend beyond the vertical meridian. This was ascertained before the experiments by placing a cardboard located 30 cm in front of the screen and covering one visual field entirely; in such a situation, the subject was unable to tell whether or not a stimulus had been flashed in this visual field. The first 4 tasks involved bilateral simultaneous presentations of visual spatial information such as presented in the top 2 rows of fig. 1, while the last 3 also of this series involved pattern information, as shown in the bottom 2 rows of fig. 1, for calculation or lexical decision. The characteristics of each task are summarized in the caption of this figure.

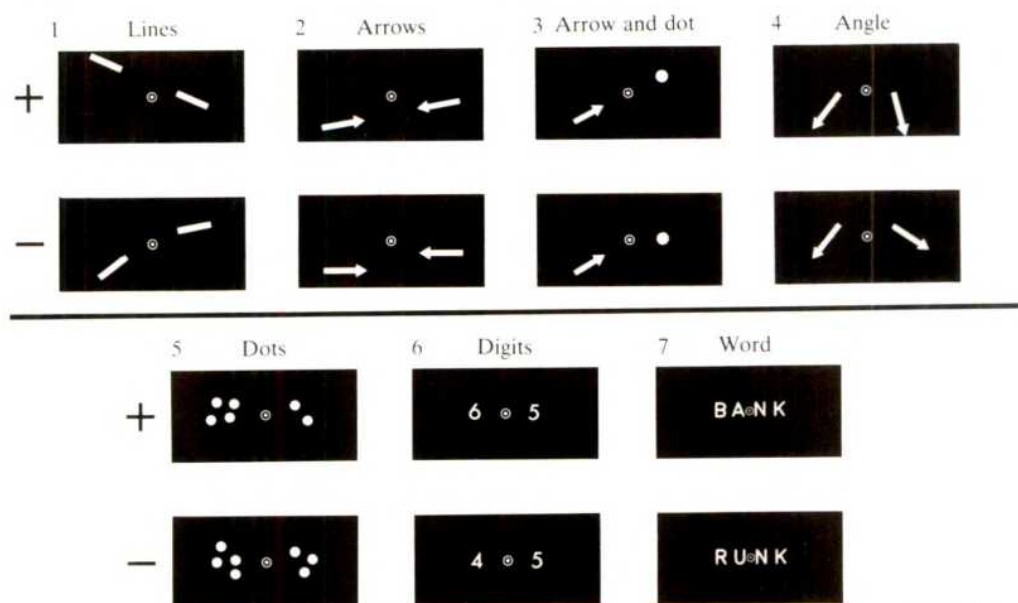


FIG. 1. Sample of the stimuli used in Tasks 1-7. The signs + and - on the left of the fig. stand for the two types of response in each task. The patients were requested to make the following decisions: (1) straight (+) or broken (-) lines? (2) Do the arrows meet head-on (+) or not (-)? (3) Does the arrow point to the dot (+) or not (-)? (4) Is the angle made by the two lines smaller (+) or larger (-) than  $90^\circ$ ? (5) Does the total number of dots amount to an even (+) or an odd (-) number? (6) Is the sum of the 2 digits larger (+) or smaller (-) than 10? (7) Is this a word (+) or not (-)?

*Procedure*

Each subject was tested in a private room, seated in front of the screen with the head supported by a chin-rest so that the eyes were at the level of the black central fixation point. The subjects were requested to hold their legs and feet apart, to keep their teeth together and the lips closed, and the

nonresponding hand lay on the side of the table with no contact with the response panel. This served the purpose of avoiding any potential transfer of information between the two sides of the body. The subjects wore headphones that masked external noise, and an independent observer monitored the subjects' eyes to control for eye movements.

A trial started with the signal 'ready' by the experimenter to warn the subject to fixate on the central dot. About 1 s later, 2 stimuli simultaneously appeared, in each visual field, and the subject was required to make a manual response, according to the instructions, by moving the hand from the resting position to the appropriate key. Both speed and accuracy were stressed in the instruction, and the subjects were reminded from time to time of the importance of fixating the central point, two procedures with which they were highly familiar. Each task comprised two experimental sessions preceded by practice trials. The responding hands were counterbalanced across sessions. N.G. responded with the right hand in the first session and the left hand in the second session of the odd-numbered tasks, and the opposite order prevailed in the even-numbered tasks. L.B. was tested with the reverse arrangement.

#### *Tasks 1-4*

In the first 4 tasks, the subjects were requested to make judgements that necessitated establishing relationships between the stimuli appearing in each visual field, and they involved simple visual-spatial processes.

#### *Method*

A sample of the stimuli used in the first 4 tasks is shown in fig 1. *Task 1*: 2 lines appeared, 1 in each visual field, and the subject had to decide whether they formed a straight or a broken line. *Task 2*: 2 arrows pointing towards the vertical meridian were presented, 1 in each visual field, and the subjects had to decide whether the arrows would meet head on or not. *Task 3*: an arrow and a dot appeared simultaneously, 1 in each visual field, and the subject was requested to decide whether or not the arrow pointed right at the dot. *Task 4*: 2 arrows pointing laterally were presented, 1 in each visual field, and the subject had to decide whether the angle formed by the 2 lines was smaller or larger than 90°. There were 12 instances of stimulus display for each type of response in each task. Within a task, the stimuli were made out of the same half-parts for each type of response. For instance, in Task 4, each of the 12 arrows appearing in each visual field served for both response types, and it was a combination of the two half-parts that determined whether the angle was larger or smaller than 90°. There was therefore no correlation between the orientation of an arrow in either visual field and the angle described by the 2 arrows. Each of the 12 instances of stimulus display were presented 4 times for a total of 96 experimental trials run once with each responding hand. Thus each task comprised 192 experimental trials, preceded by 12 practice trials before each session. Each task was run independently, and the stimulus were presented for 150 ms.

#### *Results*

The patients indicated that they found the tasks easy to perform, and no sign of hesitation or confusion was apparent in their behaviour. They responded quasi-automatically, and they were generally aware of making an error when they pressed the wrong key. Except on 3 occasions for N.G. and 2 occasions for L.B., the patients sustained steady fixation during the course of a trial in all the tasks.

The results are shown in Table 1, for each patient and each task, with the mean reaction time (RT), the SEM, and the percentage of correct responses. These data are averaged over the responding hand and over the two types of response, as a preliminary analysis of variance, using trials as random factors (Winer, 1971), indicated no significant main effect and interaction associated with these variables

TABLE 1. REACTION TIMES, SEM, AND PERCENTAGE OF CORRECT RESPONSES IN EACH OF THE FIRST 4 TASKS

|                  | <i>N.G.</i>                 |            |                  | <i>L.B.</i>                |            |                  |
|------------------|-----------------------------|------------|------------------|----------------------------|------------|------------------|
|                  | <i>RT*</i><br>( <i>ms</i> ) | <i>SEM</i> | <i>% correct</i> | <i>RT</i><br>( <i>ms</i> ) | <i>SEM</i> | <i>% correct</i> |
| 1. Lines         | 1106                        | 21.72      | 91.14            | 968                        | 19.79      | 95.83            |
| 2. Arrows        | 1104                        | 29.38      | 79.69            | 940                        | 20.17      | 95.31            |
| 3. Arrow and dot | 1149                        | 24.87      | 76.56            | 1075                       | 15.07      | 93.23            |
| 4. Angle         | 728                         | 23.53      | 98.95            | 988                        | 15.16      | 96.88            |

\*RT = reaction times of correct responses, averaged over responses hand and response type; percentage of correct responses is over 192 trials; SEM  $\pm$  standard error of the mean.

in latency and accuracy ( $F_s(1, 194) < 1$ ). A stringent criterion of significance, consisting of halving the obtained statistic value, was used as recommended by Winer (1971) for the analysis of individual data. The main finding from these tasks was that both N.G. and L.B. were capable of responding in about 1s after stimulus onset, in each of the tasks, at a level of accuracy which was significantly above chance ( $\chi^2(1) > 9$ ,  $P < 0.01$  in all but one case: N.G.'s arrow-and-dot task,  $\chi^2(1) = 6.52$ ,  $P < 0.05$ ). These results suggest that, despite their commissurotomy, the patients had available for processing an undivided representation of the whole display on the basis of which they could establish a relationship between the information initially segregated between the hemispheres, not only with respect to the orientation of the 2 stimuli (Tasks 1–3) but also at a more qualitative level when determining the angle described by the 2 arrows (Task 4).

In an attempt to obtain additional information about the patients' performance, some stimuli were again presented tachistoscopically after the 4 tasks were completed, and the subjects were asked to describe verbally what they saw. N.G. never could provide accurate information about the left part of the display while she readily described the nature, position, and orientation of the right part. When she was requested to indicate the orientation of the left arrow by telling the hour it would depict on a clock, she could not answer verbally but could draw it with either hand, while she had no difficulty providing a correct answer for the right-field arrow. Although telling the time from the orientation of an arrow involves processing requirements different from those involved in the 4 tasks, N.G.'s failure to provide any information about the left arrow nonetheless indicates that the left hemisphere had no knowledge of the nature of the information received by the right hemisphere. By contrast, L.B. was able to come up with accurate verbal answers about the information presented in each visual field, but his responses concerning the left part of the display were never given as spontaneously as they were for the right, and they took at least 5s as opposed to 1s for information presented in the right field. This suggests that, at the time a decision was made in the experimental sessions, the left hemisphere had not yet had access directly to the information received by the right hemisphere.

The results of these 4 tasks suggest that the information initially segregated in each hemisphere could be assembled and integrated for the production of a correct response. Part of this information was not available for verbal report at the time a decision was made, and the left hand was not faster than the right hand in producing the response. These two facts may indicate that neither hemisphere had access to the whole information and that the integration may have taken place at a level of processing not directly accessible to conscious awareness, although the outcome of this integration could be used to make a voluntary response. The present evidence is concerned with visuospatial information and orientational operations and, as such, extends earlier demonstrations of subcortical transmission (Trevarthen and Sperry 1973; Holtzman, 1984). This evidence was obtained with simultaneous presentation of bilateral information, and with an immediate response, by contrast to long or successive presentations used in previous studies, suggesting a capacity to relate visuospatial information readily across the visual field in the absence of forebrain commissures. The nature of the information presented, and of the operations required, may be within the functional capacity of subcortical structures, and may not have involved cortical mediation, which could suggest that the present findings are not conclusive with respect to the integration of hemisphere activity through subcortical processes. The subsequent tasks were therefore directed toward examining whether this integration could be illustrated in more demanding cognitive tasks requiring cortical mediation.

#### *Tasks 5-7*

Tasks 5 to 7 served the purpose of determining to what extent subcortical involvement in coordinating hemisphere activity can mediate the integration of information received by each hemisphere in tasks that call for acquired skills necessarily requiring cortical mediation.

#### *Method*

A sample of the stimuli used in Tasks 5, 6, and 7, is presented in the bottom 2 rows of fig. 1. In *Task 5*, the patients were presented with dots in each visual field (from 1 to 4 in each field), and they had to decide whether the total number of dots amounted to an even or an odd number. In *Task 6*, 2 digits were simultaneously presented, 1 in each visual field, and the patients had to decide whether the sum of the 2 digits was larger or smaller than 10. The digits of each pair were chosen so as to minimize as much as possible clues concerning the probability of their sum being larger or smaller than 10, and the digits 1 and 9 were not used. *Task 7* consisted of a lexical decision task. A 4-letter high-frequency word, or a 4-letter pronounceable nonword, was presented in the centre of the visual field so that the first 2 letters fell in the left visual field and the last 2 letters in the right visual field. Ten words were used and the nonwords were created by combining the first 2 letters of a word with the last 2 letters of another word, with the constraint that the combination resulted in a pronounceable nonword (e.g., RUNK was made from the words RULE and BANK). This procedure equated the type and number of appearances of each 2 letters within each visual field across types of response and made it impossible for the subjects to infer that a word or a nonword had been presented from the 2 letters appearing in one visual field. By contrast with the other stimuli, there was no gap in the centre such that the 4 letters formed a continuous word (or nonword). The stimuli subtended  $3.54^\circ$  of visual angle, with each letter separated by  $1.18^\circ$  such that the second and third letters were centred

0.59° from fixation. This was thought sufficient to ensure projection only to the contralateral hemisphere as Sperry (1968a) has shown that the midline division along the vertical meridian is quite precise, without gap or overlap, in N.G. and L.B. Evidence from human anatomy indicates a sharp splitting of retinal projections (Harrington, 1981), and earlier studies with commissurotomed patients, using chimeric stimuli centrally presented and spanning 1° of visual angle, showed exclusively contralateral hemispheric projection of information appearing within 0.5° from fixation (e.g., Levy *et al.*, 1972).

As in the previous series, each task was conducted in 2 experimental sessions, each with a different hand responding, preceded by practice trials. There were 10 instances of stimulus display for each response type in each task (with some repetition in a different pattern in the case of dots), and each was repeated 5 times for a total of 100 trials per experimental session. Before carrying out each task with the stimuli straddling the central fixation point, the same tasks were conducted in unilateral presentation, with the stimuli appearing entirely within the right or the left visual field. This served to determine the respective capacity of each hemisphere for calculation and lexical decision. Two experimental sessions comprising 80 unilateral presentations each were conducted before each task. A stimulus was presented at random in one field or the other within a session, with its inner edge located 2.5° from fixation.

All other aspects of these tasks were similar to those prevailing in Tasks 1 to 4, except that Task 6, which involved only 1 digit in one visual field in the bilateral condition, was conducted at a 100 ms exposure.

## Results

The results of the 3 tasks for the *unilateral* condition are presented in Table 2, as a function of visual field. Both patients performed significantly above chance in each visual field and in each task, thus confirming earlier findings that each disconnected hemisphere can perform simple calculation (Sperry, 1968b) and lexical decision (Zaidel, 1982). A comparison of visual field accuracy within each task for each subject revealed no significant difference (all  $\chi^2$  (1) < 2.5,  $P$  > 0.10). Both patients responded faster to left than to right visual field presentations in the dot-counting task, and this difference reached a reliable level of significance in N.G.

TABLE 2. REACTION TIMES, SEM, AND PERCENTAGE OF CORRECT RESPONSES IN THE UNILATERAL CONDITION OF TASKS 5, 6, AND 7

|           |     | N.G.       |       |           | L.B.       |       |           |
|-----------|-----|------------|-------|-----------|------------|-------|-----------|
|           |     | RT<br>(ms) | SEM   | % correct | RT<br>(ms) | SEM   | % correct |
| 5. Dots   | LVF | 1308       | 45.10 | 83.00     | 1391       | 45.03 | 86.50     |
|           | RVF | 1451       | 47.93 | 80.50     | 1512       | 46.12 | 81.00     |
| 6. Digits | LVF | 1140       | 31.12 | 93.00     | 1090       | 30.15 | 92.50     |
|           | RVF | 1106       | 29.98 | 95.00     | 1043       | 28.10 | 95.00     |
| 7. Words  | LVF | 1380       | 43.51 | 76.50     | 1206       | 26.89 | 80.50     |
|           | RVF | 1172       | 40.18 | 82.00     | 1075       | 34.37 | 85.50     |

RT = reaction time; LVF = left visual field; RVF = right visual field; SEM = standard error of the mean.



TABLE 3. REACTION TIMES, SEM, AND PERCENTAGE OF CORRECT RESPONSES IN THE BILATERAL CONDITION OF TASKS 5, 6, AND 7

|           | <i>N.G.</i> |            |                  | <i>L.B.</i> |            |                  |
|-----------|-------------|------------|------------------|-------------|------------|------------------|
|           | <i>RT</i>   | <i>SEM</i> | <i>% correct</i> | <i>RT</i>   | <i>SEM</i> | <i>% correct</i> |
| 5. Dots   | 1201        | 36.69      | 84.00            | 1356        | 30.70      | 89.50            |
| 6. Digits | 1036        | 19.51      | 94.00            | 987         | 17.72      | 89.50            |
| 7. Words  | 1124        | 29.52      | 70.50            | 1046        | 25.81      | 75.00            |

RT = reaction time.

( $F(1,78) = 4.06$ ,  $P < 0.05$ ), but not in L.B. ( $F(1,78) = 2.72$ ,  $P > 0.05$ ). There was no visual field difference on the digit task, and, although presentation in the right visual field led to faster and more accurate lexical decision than left presentations in both patients, this difference did not reach a reliable level of significance ( $F_s(1,78) < 2$ ,  $P > 0.10$ ).

Table 3 presents the results of Tasks 5, 6, and 7 for the 2 patients in the *bilateral* condition. It shows that when the information was initially segregated such that each hemisphere received only part of the information, both patients were capable of responding at above chance level. The lowest level of accuracy was obtained in the lexical decision task in both N.G. and L.B., but this level was significantly above chance ( $\chi^2(1) > 4.5$ ,  $P < 0.05$ ). A comparison of reaction times between unilateral and bilateral conditions, using the procedure recommended by Winer (1971) for unequal numbers of observations, showed that both patients responded faster in the bilateral than in the unilateral condition, but not significantly so. Thus even in tasks involving pattern vision and relatively demanding cognitive processing, the 2 patients were capable of attending simultaneously to both fields of presentation, of integrating the information received by each hemisphere, and of making correct decisions on this information.

The nature of the mechanisms underlying this performance and their anatomical substrates remain unknown, but some aspects of the patients' behaviour in subsequent testing may be instructive in this respect. N.G. was again presented tachistoscopically with words and nonwords straddling the fixation point, but was not requested to make a lexical decision at first. In such a condition, she could only name the 2 letters appearing in the right visual field and was unable to provide any information about the part of the display falling in her left visual field. In another condition, she was asked first to make a lexical decision and then to report verbally on what was presented. In such a case, she responded with a word, the last 2 letters of which were correct if a word was actually presented. For instance, to the presentation of the word BANK, she answered 'INK ... PINK ... I don't know'; to the word TEST, 'BEAST ... FEAST'. By contrast, she only named the last 2 letters when she had first responded that a nonword had been presented. These verbal responses suggest that N.G. (more precisely, her left hemisphere) was aware of the outcome of her decision, but not of the actual word on which this decision

was made. Knowing that a word had been presented, she was using the last 2 letters received by her left hemisphere along with her lexical knowledge to produce a word consistent with the information present in her left hemisphere. She never produced the correct word, however. Similar observations were made in the bilateral condition of the digit task (Task 6). N.G. never succeeded in naming the digit appearing to the left of fixation, whereas she was accurate in naming the right digit. Neither could N.G. tell the exact sum of the 2 digits but she accurately reported whether it was more or less than 10. The behaviour of L.B. in this subsequent testing differed from that of N.G. He could immediately report the 2 letters appearing on the right, but, in most instances, he was also capable of naming the word presented in the centre of the visual field. This was not done spontaneously, however, and sometimes only after 60 s or more of what appeared deep and effortful thinking. When queried about his strategy, L.B. replied that he 'went through the letters of the alphabet until something clings'. Whether or not this was actually the strategy used by L.B., it could not underlie the lexical decision in the experimental sessions, as this decision was made too quickly for such a scanning of the alphabet to take place. In addition, an examination of his reaction times indicated no variation as a function of the letters composing the words. For example, his responses to the words **BANK** and **RULE** were made equally fast even though the first 2 letters were at the beginning of the alphabet for the former and at the end for the latter. Moreover, if such a strategy had underlain L.B.'s performance, it would also have implied very long latencies to make a nonword response, but this was not the case.

The fact that both patients could report spontaneously only the 2 letters appearing in the right visual field confirms that they were accurately fixating the central point and that the information was effectively segregated between the hemispheres as intended; it also suggests that accurate decisions could be made by both patients in the absence of conscious awareness of what the entire information actually was. This cross-integration was shown in tasks calling for highly practiced skills on familiar information. The last task was designed to determine whether a similar cross-integration would be achieved in an unfamiliar task.

### *Task 8*

This task involved a colour-shape discrimination using stimuli similar to those shown in fig. 2. The stimuli were made by combining 1 of 2 colours (green or blue) with 1 of 2 shapes (circles or cross), in all possible combinations, and they were presented in such a way that the colour appeared on one side of fixation and the shape on the other. Two combinations of colour and shape were assigned to one type of response (blue-circle and green-cross) and the other two conditions to the other type of response (blue-cross and green-circle). With this arrangement, neither the colour alone nor the shape alone was a sufficient clue to respond correctly. Knowledge of both the colour and the shape, which were projected to different

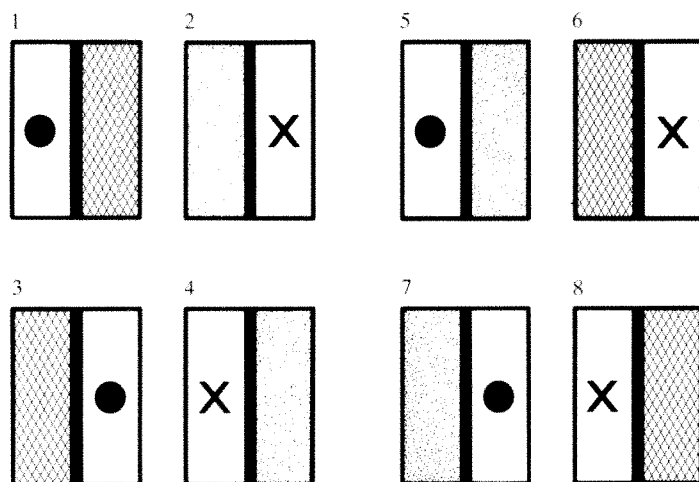


FIG. 2. Analog representations of the stimuli used in Task 8. In the experiment, the shapes appeared as shown here while the space occupied by the grid and the random dots appeared as blue and green, respectively. Stimuli 1 to 4 were assigned to one response key and stimuli 5 to 8 to the other response key.

hemispheres, was necessary to make an accurate decision, and this could be achieved only by combining the two halves of the stimulus at some stage during processing.

### Method

There were 8 stimuli in all (*see* fig. 2), and they appeared in the centre of the visual field such that each half projected to different hemispheres. They subtended a visual angle of  $5.5^\circ \times 4^\circ$ , with the blue and green of equal luminance ( $42 \text{ cd/m}^2$ ); the circle and the cross were of equal area and appeared as black on a white background ( $117 \text{ cd/m}^2$ ). The vertical stripe separating the two halves fell exactly on the vertical meridian and subtended a visual angle of  $0.33^\circ$ . Each stimulus was presented 16 times for a total of 128 trials per experimental session. Two such sessions were conducted, one with the right and the other with the left hand responding. The display was presented for 100 ms. The subjects were initially given practice with the stimuli appearing entirely within one visual field or the other, in order for the subjects to learn to associate the displays with their corresponding responses. This was done in 2 sessions of 64 trials each, 1 with each hand, after the subjects had been given 5 min to look at the 8 stimuli in free viewing conditions. N.G. failed to learn to associate the stimuli with their respective response keys in the unilateral condition, and she was not tested in the bilateral condition. L.B. readily learned the associations, and he could perform the unilateral task at about equal efficiency in the left and the right visual fields (RT and % Correct, averaged over both responding hands: 1107 ms, 98.4% for the right visual field, and 1202 ms, 91.6% for the left visual field).

### Results

The results of the bilateral condition for L.B. are shown in Table 4, as a function of the responding hand. L.B. performed the task at a high level of efficiency, and although he was faster with his right than with his left hand, the difference was not significant ( $F < 1$ ). He could respond within 1 s on average, with no sign of hesitation or confusion.

TABLE 4. REACTION TIMES, SEM AND PERCENTAGE OF CORRECT RESPONSES, AS A FUNCTION OF RESPONDING HAND, IN THE COLOUR-SHAPE DISCRIMINATION TASK BY L.B. (TASK 8)

|           | <i>Left hand</i> | <i>Right hand</i> |
|-----------|------------------|-------------------|
| RT* (ms)  | 981.08           | 923.34            |
| SEM       | 22.79            | 22.93             |
| % correct | 96.09            | 97.66             |

\*Reaction time.

## DISCUSSION

Commissurotomy physically disconnects the two cerebral cortices, depriving the hemispheres of their main means of communication, and the resulting disconnection syndrome has been viewed as creating two separate minds or spheres of conscious awareness operating in isolation within the same cranium (Sperry, 1984). The present study was deliberately framed so as to encourage exchange of information and cooperation between the two hemispheres. The results showed that, in such conditions, the information initially segregated between the two disconnected hemispheres could be combined and acted upon in a unified manner, suggesting that the outcome of the operations independently carried out by each hemisphere converged towards structures where they could be put in relation and processed simultaneously. The two hemispheres were capable of attending to their respective field of vision, of accurately encoding the incoming information, and of uniting their resources towards a common purpose, which departs from predictions based on the current understanding of the callosal disconnection syndrome. These results may thus offer a different viewpoint on the effects of sectioning forebrain commissures in human subjects, and they suggest greater capacity of the commissurotomed brain to integrate the activity of its two hemispheres than had been previously reported. Before considering some of the mechanisms that may underlie the patients' performance and discussing the implications of these findings, it is necessary to examine whether the results are reliable and reflect what the study was designed to evaluate.

### *Methodological considerations*

The present results show unequivocally that information presented simultaneously in each lateral visual field could be put in relation and responded to in a unified manner. The experiments were designed such that successful performance would reflect the mediation of subcortical processes, but it must be ascertained that the patients did not use other means of uniting the bilateral information. Two possibilities must be examined in this respect: cross-cueing and eccentric fixation.

Cross-cueing refers to strategies to which some patients, especially L.B., resort to exchange information between the hemispheres through some type of signal elaborated by one hemisphere and picked up by the sensory organs projecting to the other hemisphere (Gazzaniga and LeDoux, 1978). Several precautions were

taken to prevent the patients from having recourse to such a strategy, including the separation of the limbs, and the use of a timed response and of stimuli that did not lend themselves to direct transformation into some type of cueing signal. Even if such a transformation could be achieved, a cross-cueing strategy would require that information presented in one field be encoded, interpreted, transformed into a signal which must then be transmitted by the receiving hemisphere and which the other hemisphere must encode, interpret, transform into the same 'language' as the information already received, put the two sides of the stimulus in relation, make a decision and finally execute a response, all this in about 1 s. It is hardly conceivable that all these operations could be accomplished in such a short time. It is also doubtful that the stimuli of Tasks 1 to 4 could have been transformed into a cueing signal containing information about the orientation, direction and position of the line or arrow. It is therefore reasonable to assume that cross-cueing did not underlie the patients' performance in the present study.

Another factor that might account for the present results is the possibility of eccentric fixation, whereby all the information would have been projected to only one hemisphere because the patients would have deviated their eyes toward one field or the other. The direct monitoring of eye movements by an independent observer is a crude method for controlling fixation and, even if the patients displayed sustained fixation, this is not sufficient to guarantee accurate fixation. Both patients have had long practice with this procedure and are quite aware of the importance of fixating the central dot. In fact, the procedure used in the present study was the same as that prevailing in previous tachistoscopic studies with these patients and which yielded evidence of hemisphere disconnection. Moreover, in the task where no gap separated the bilateral information (Task 7), and where accurate fixation was most crucial, both patients displayed evidence that they were accurately fixating the centre of the visual field. They could immediately report only the 2 letters falling in the right visual field but not those falling in the left visual field. Had their eyes deviated from the centre, they would have either reported the whole word or the 4 letters if they were looking to the left of the stimulus, or nothing if they were looking to the right. These 2 patients have so far been quite reliable in maintaining fixation, and the results of Task 7 confirmed that they were following the instructions as requested.

It is thus justified to regard the present findings as free of procedural artefacts and as reflecting the involvement of subcortical structures in integrating the information initially divided between the two hemispheres.

#### *Subcortical integration of hemisphere activity*

One startling aspect of the results is that both N.G. and L.B. were capable of making accurate decisions in the absence of conscious awareness of the whole information on which the decision was made. This was typically the case in the digit and lexical decision tasks. For example, in the latter, only the last 2 letters could be reported verbally within the time needed to make a decision. Had the

lexical decision been made within the left hemisphere, both patients would have been able to provide spontaneously the name of the word that was presented. On the other hand, there is no reason to believe that the right hemisphere had more access to the last 2 letters than the left hemisphere to the first 2 letters, and it is thus most improbable that the decision was made within the right hemisphere. By contrast, at least the left hemisphere was aware of the outcome of the decision, as indicated by the patients' capacity to tell whether a word or a nonword had been presented, and the fact that the patients responded as quickly with the left as with the right hand may indicate that the right hemisphere was also aware of the outcome of the decision even if it could not provide information about it. Thus the performance of the patients indicates the joint occurrence of a unified response *and* a disunified awareness of the information divided between the two hemispheres.

It is this joint occurrence of two apparently contradictory events that constitutes the crucial finding of this study and provides new information about the disconnection syndrome. Despite each hemisphere being cut off from the information received by the other, the commissurotomed brain acted as a function of the information received by *both* hemispheres. On the one hand, the presence of separate left and right domains of conscious awareness concurs with the classical disconnection syndrome. When the patients are required to respond as a function of the *content* of the information present in each hemisphere, they typically show an inability to exchange information between the hemispheres, and this was observed in the present study with N.G. and, at least in the few seconds following stimulus presentation, with L.B. On the other hand, the unity and coherence of *behaviour*, typical of these patients outside the laboratory, was demonstrated, in the laboratory, by their capacity to produce an integrated response. This was achieved in conditions where the two hemispheres received different information and, therefore, were not sharing the same experience (*see* Sperry, 1984), and where both hemispheres had to process their respective input simultaneously, thus ruling out the involvement of 'metacontrol' whereby only one hemisphere would be operative (*see* Levy and Trevarthen, 1976).

This subcortical coordination of hemisphere activity may thus underlie the behavioural integration displayed by commissurotomed patients in their daily activities, allowing them to relate different parts of the visual field and to maintain a unity of purpose in their action. An absence of disconnection syndrome outside the laboratory was apparent soon after the operation in most patients (Sperry, 1984), and the present performance may thus reflect a basic property of the commissurotomed brain and not a functional reorganization of neural pathways. This suggestion is admittedly speculative, however, as the apparent normality of the patients' behaviour was not the object of empirical investigation until recently and, complete commissurotomy being no longer performed, it may be impossible to test the validity of this suggestion in human subjects. Recourse to experimentation on animals may then be required to examine whether subcortical

integration evolves in the years following commissurotomy and to identify the subcortical structures actually involved in this integration.

### *Implications*

Although drawing on findings from commissurotomed patients for inferences about the intact brain requires caution, the present results may be consistent with the view that brainstem areas are deeply involved in the control of behaviour and intimately interact with cortical structures in the elaboration and regulation of cognitive information processing. This was suggested by Fessard (1954) and Penfield and Roberts (1959) who pointed out the crucial role of the upper brainstem not only in contributing alerting and arousing components to cortical activity but also in participating in content-oriented processes. Studies of patients born without the corpus callosum (Ettlinger *et al.*, 1972; Jeeves, 1965, 1986; Milner and Jeeves, 1979) also argue for a critical role of midbrain structures in interhemispheric integration while indicating definite limitations in subserving this integrating function compared with forebrain commissures (Jeeves, 1979). In addition, findings of cognitive deficits following damage of subcortical structures (e.g., Brown, 1977; Castaigne *et al.*, 1981) suggest that these structures contribute significantly to operations underlying cognitive information processing.

Recent anatomical evidence indicates an intricate network of neural connections between visual cortical areas and subcortical structures that provide for complex and diverse exchange of information and reciprocal influence (Tigges and Tigges, 1985). The study of commissurotomed patients extends these suggestions by showing that subcortical structures may have the functional capacity to subserve the integration of information at a visuospatial and higher-order cognitive level. However, this integration was far from perfect and was performed without reaching conscious awareness, confirming the limitations of these structures which may transmit only the outcome of their operations. In fact, considerable reduction and impoverishment of information may be expected given the relatively small subcortical space compared with cortical areas. The large surface devoted to the mapping of the visual field in the cortex (Van Essen, 1985) may make unnecessary a detailed representation of visual information at a subcortical level, which may be why these structures are inefficient at transferring the total content of a percept from one hemisphere to the other (Bogen, 1985; Holtzman, 1984; Myers and Sperry, 1985; Sergent, 1986). However, processes involving a many-to-one, rather than a one-to-one mapping of the information may be within the functional capacity of subcortical structures, and such a loss of information may prove to be a necessary requirement for achieving an integration. It is an empirical question left for future investigation to determine the limits of subcortical structures in subserving this function, in terms of both load and nature of information they can process, integrate and transmit.

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# ELECTROPALATOGRAPHIC ANALYSIS OF APRAXIA OF SPEECH IN A LEFT HANDER AND IN A RIGHT HANDER

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## SUMMARY

Two cases with 'pure' apraxia of speech are reported. The articulatory disturbances were quite similar. One of the two cases was a left-handed male with a subcortical haemorrhage and the other a right-handed male with a cerebral infarct. The MRI and CT scans showed that the first case had a lesion that mainly involved the right precentral gyrus and its deep white matter, and that the second had a lesion mainly affecting the lower parts of the left precentral and postcentral gyri and their deep white matter. These findings and a literature review suggest that a corticosubcortical lesion of the lower part of the left precentral gyrus in most right handers and a lesion of the symmetric region in the right hemisphere in some left handers cause apraxia of speech.

The omission errors for sounds articulated by the tongue and the hard palate were analysed using electropalatography, which records visually the dynamics of the palatolingual contact. The results demonstrated that there were three kinds of omission errors: true omissions (no palatolingual contact); omissions with incorrect contact (palatolingual contact for a different sound or undifferentiated sound); and omissions with correct contact (correct palatolingual contact for a target sound). The latter two types of omission error were observed for initial consonants and they were probably caused by a delay in air flow. The patients also showed a tendency to substitute one of the two consonants /t, tʃ/ for other sounds, which suggested that they had difficulty in the inhibition of tongue activity.

## INTRODUCTION

It has been known that a unilateral hemisphere lesion uncommonly causes disturbance limited to speech output involving neither auditory nor reading comprehension nor writing disturbance. The syndrome has been variously termed aphemia (Broca, 1861; Bastian, 1898), pure anarthria (Marie, 1906), pure word dumbness (Wernicke, 1906) or pure motor aphasia (Dejerine, 1914). We will use the term 'aphemia' for brevity.

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Aphemia represents at least two types of disturbance. Some patients with aphemia show an inability to articulate all except a very limited set of phonemes or words (Dufour, 1895; Ladame and von Monakow, 1908; Souques, 1928), while others are able to utter most phonemes but show many articulatory errors such as substitutions, additions, omissions and distortions (Denny-Brown, 1965; Lecours and Lhermitte, 1976; Tonkonogy and Goodglass, 1981). These errors are characterized by inconsistency in two ways: phonemes are articulated incorrectly at one time but correctly at another; and errors are not always the same. The second type of disturbance has been reported after recovery from the first (Denny-Brown, 1965; Lecours and Lhermitte, 1976) but not in others (Dufour, 1895; Souques, 1928). F. L. Darley (unpublished) designated the second type 'apraxia of speech'. These two types of disturbance are different from dysarthria arising from bilateral damage of the corticobulbar tracts, the cerebellum or the lower motor neuron whose speech has normal length and where errors tend to be consistent.

Although the articulatory characteristics of apraxia of speech associated with aphasia have been thoroughly studied by systematic phonetic analysis (Shankweiler and Harris, 1966; Johns and Darley, 1970; Trost and Canter, 1974), those of 'pure' apraxia of speech have not been well studied. Even in the well described case with pure apraxia of speech (Lecours and Lhermitte, 1976), the size of the speech sample was not large enough for systematic phonetic analysis.

In the present paper, 2 cases of aphemia (pure apraxia of speech) will be reported. They uttered a very limited number of phonemes at an early stage. At a later stage, they began to produce most phonemes but with numerous articulatory errors. Thus their disturbance at its later stage is well covered by the term 'apraxia of speech'. The utterances of the 2 cases were studied systematically by auditory phonetic analysis to elucidate the articulatory characteristics of apraxia of speech.

Among the various kinds of articulatory errors in apraxia of speech, substitution errors have attracted most attention in the literature. Omission errors, however, are also supposed to characterize apraxia of speech. Electropalatography was employed to observe directly the palatolingual contact during omission errors of our 2 cases in order to clarify the characteristics of this type of error.

The location of the lesion responsible for aphemia or apraxia of speech is still uncertain. Lecours and Lhermitte (1976) have suggested that, in the right-handed, a lesion of the lower part of the left precentral gyrus causes the syndrome. However, a number of cases are needed to confirm the site of the lesion responsible for the syndrome in the right-handed. In the left-handed, so far as we know, no study has established the site of the responsible lesion. One of the 2 cases in this study was left-handed, and the other right-handed. Magnetic resonance imaging (MRI) and computerized tomography (CT) were administered to localize the site of their lesions.

## CASE HISTORIES

*Case 1 (K. O.)*

A 27-yr-old left-handed man, a high school graduate, without prior medical problems, had a subcortical haemorrhage in the right frontal lobe on June 2, 1984. The patient was left-handed from infancy. The left hand was used for all activities except writing and eating with chopsticks. As for these two activities, he had used his left hand at first, but was forced to change to his right hand in childhood. He was left-handed except for writing on the Oldfield Handedness Battery (Oldfield, 1971). His parents and 3 siblings were all right-handed.

Neurological examination on admission (June 2, 1984) revealed impaired consciousness, a left hemiplegia including the lower face, deviation of the tongue to the left, and a left hemihypaesthesia primarily affecting the left upper limb. Two days later he was alert, but with a mild hemiparesis predominantly in the left upper limb. He uttered only /o/, /N/ and /hai/, the latter two meaning 'yes' in Japanese. Angiography disclosed an arteriovenous malformation, which was fed from the right precentral artery and was drained to the right superficial sylvian vein.

The patient was operated upon on June 6, 1984. A craniotomy was performed in the right frontoparietal region. A semiliquid haematoma ( $6 \times 5 \times 4$  cm) and the nidus were removed. Neurological examination 1 month after onset showed a mild left-sided lower facial weakness, deviation of the tongue to the left and a left arm monoparesis. There were no signs of left hemihypaesthesia. Two months after onset, neurological examination showed a mild left-sided lower facial weakness and a mild paresis of the left arm. Otherwise examination was normal. Tongue deviation was not present. Pure tone threshold audiometry showed normal hearing levels in both ears despite a 40 dB loss in the left ear and a 15 dB loss in the right at 8000 Hz. Speech audiometry with monosyllabic speech sounds (67-A list a standardized single-syllable list for speech discrimination test by the Japanese Audiological Society) was within normal limits in both ears.

*Neurological findings.* MRI (Picker International Ltd, VISTR-MR 0.5T) was carried out with a 0.26 Tesla superconducting magnet, using the inversion recovery technique, 10 months after onset. The images (fig. 1) showed an abnormal low intensity region mainly in the right precentral gyrus and its underlying deep white matter such as the middle region of the corona radiata and the right arcuate fasciculus. CT scans parallel to the orbitomeatal line were administered with Toshiba Medical Equipment TCT-60A 1 month and 18 months after onset. They revealed findings compatible with MRI although contaminated with artefacts from the surgical clips (fig. 1).

*Language testing.* For 10 days after onset, his spontaneous speech was limited to /a/, /i/, /u/, /o/, /N/, /wN/ and /hai/ the latter three meaning 'yes' in Japanese. The patient could not even say his name. Oral repetition was severely disturbed. He could not repeat very familiar phrases such as /ohajo:/ (good morning), for which he uttered /ohooow/. However, he correctly understood questions about his illness and family. He could also comprehend oral commands, such as 'Close your eyes' and 'Open your mouth' and could carry out these commands. He had no difficulty in writing the names of common objects, although he showed a slight disturbance in writing sentences.

The Japanese edition of the Western Aphasia Battery (WAB) (Kertesz, 1982; Sugishita *et al.*, 1986) 0.8 month after onset revealed a marked discrepancy between his speech disturbance and other abilities, namely those of auditory comprehension, reading comprehension and writing (Table 1). In the spontaneous speech task, his disturbance was severe. His production was effortful and slow. Substitution, omission and distortion errors were numerous. He could utter only 9 different phonemes. Among them, 3 different phonemes happened to occur twice in his answers. These were articulated correctly at one time whereas they were misarticulated at another. However, his speech consisted of the correct number of syllables with an approximation of vowels when the target utterances were short. For example, when he was asked 'What is your name?', he uttered /'ooajapieii/, the vowels of which were all correct, though his utterance included 3 omission errors on consonants. To the question 'What is your occupation?', he responded with /anikjaNN/ for /kaijaiN/ (businessman).

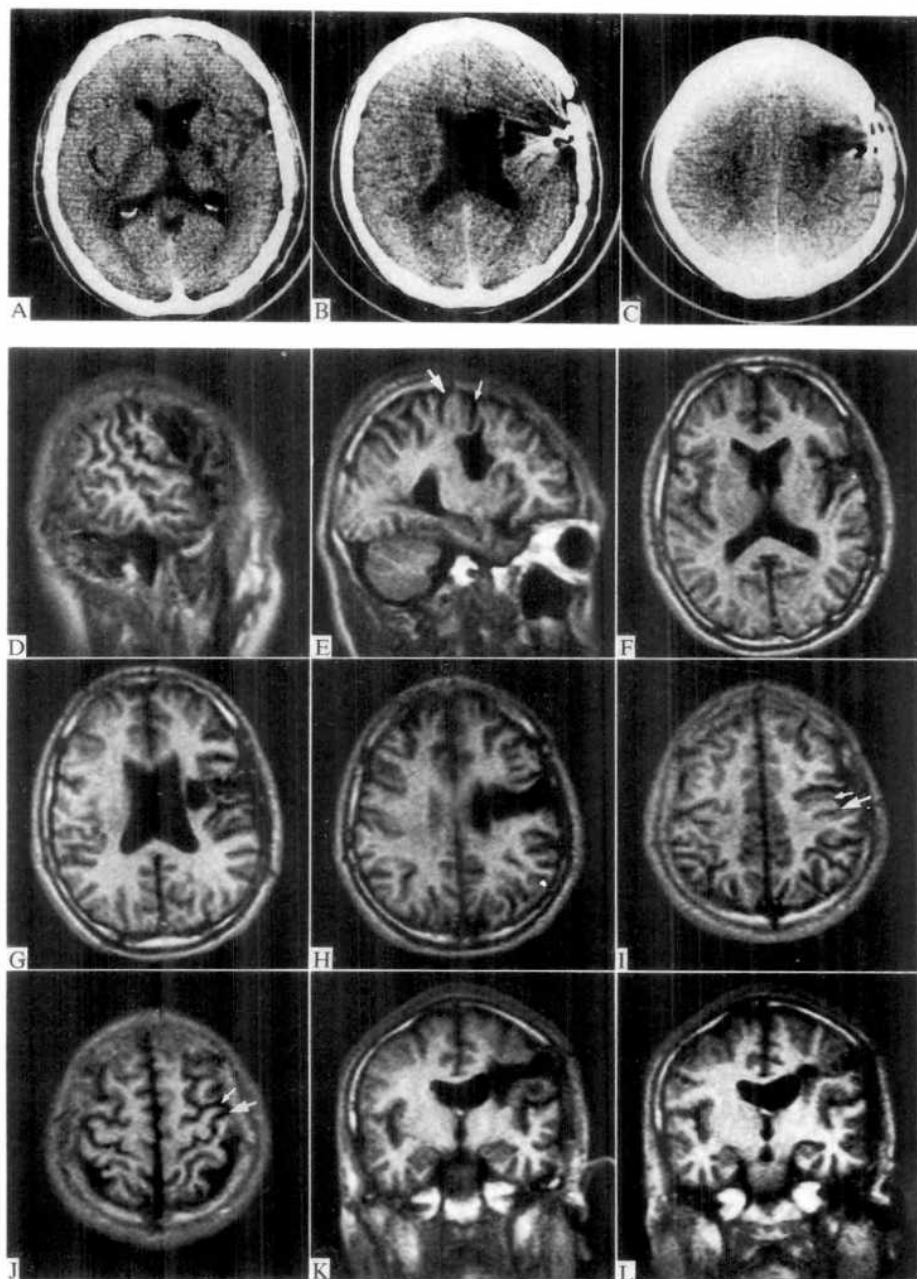


FIG. 1. A-C, CT scans from *Case 1*, 18 months after onset showing an abnormal area of low density mainly affecting the right precentral gyrus extending deeply into the underlying white matter, although artefacts from the surgical clips make the scans unclear. D-L, MRI from this case, 10 months after onset, revealing an abnormal low intensity area in the right precentral gyrus including the middle region of the right corona radiata and the right arcuate fasciculus. Right central sulcus (large arrows); right precentral sulcus (small arrows).

TABLE 1. WESTERN APHASIA BATTERY SUBSCORES (WAB)

|                            | Case 1                    |         | Case 2  |         |
|----------------------------|---------------------------|---------|---------|---------|
|                            | Interval postonset tested |         |         |         |
| Subtest category (maximum) | 0.8 mo.                   | 2.8 mo. | 1.3 mo. | 9.6 mo. |
| Spontaneous speech         |                           |         |         |         |
| Information content (10)   | 3                         | 9       | 0       | 8       |
| Fluency (10)               | 1                         | 9*      | 0       | 9*      |
| Comprehension (10)         | 9.6                       | 10      | 9.6     | 10      |
| Repetition (10)            | 3.6                       | 6.7     | 0       | 5       |
| Naming (10)                | 6**                       | 6.8**   | 0.1     | 6.5**   |
| Reading (10)               | 8.2                       | 9.7     | 6.9     | 9.4     |
| Writing (10)               | 8.5                       | 9.9     | 6       | 8.7     |
| Praxis (10)                | 10                        | 10      | 9.9     | 10      |
| Construction               |                           |         |         |         |
| Drawing (3)                | 3                         | 3       | 3       | 3       |
| Block design (0.9)         | 0.9                       | 0.9     | 0.9     | 0.9     |
| Calculation (2.4)          | 2.4                       | 2.4     | 2.4     | 2.4     |
| Raven's score (3.7)        | 3.4                       | 3.5     | 2.9     | 2.8     |

\*Fluency evaluation in the WAB includes phrase length, melody, syntax, paraphasia and word-finding difficulty. The high scores in fluency are due to lack of agrammatism and word-finding difficulty. \*\*The relatively low scores in the naming task are due to substitution errors in sounds.

His abilities to repeat and to read aloud were also severely impaired. During the repetition task, he uttered /anana/ for /banana/ (banana) and /enwaanatte:a:su:/ for /denwaganatteimasu/ (The telephone is ringing). He had no response (naming difficulty) to 1 out of 20 objects in the naming task and articulatory errors to 19 out of the 20 objects. As illustrated in these examples, vowels were less affected than consonants. The patient showed many articulatory errors, such as substitutions, omissions, additions and distortions of sounds. Self-correction was seldom observed.

On the other hand, auditory comprehension, reading comprehension and writing were intact. Auditory comprehension of words was tested with 76 items, and in this he had a perfect score. With 'Yes-No questions' to assess auditory comprehension of sentences such as 'Do you eat a banana before you peel it?' and 'Is a horse larger than a dog?', he correctly responded to 19 out of 20 questions. Oral sequential commands varied from relatively short and easy commands, such as 'Raise your hand', to rather complicated ones such as 'Put the comb on the other side of the pen and turn over the book.' Ten of these 11 commands were correctly executed. His reading comprehension was also nearly intact. In the task where he read sentences and then chose the missing words or phrases, he correctly answered 7 out of 8 items. His writing ability was also quite well preserved, and he wrote 3 sentences describing 10 objects with only 2 spelling errors when requested to describe a presented picture.

The WAB was retested 2.8 months after onset (Table 1). Though his speaking ability improved to the extent that he often uttered short sentences, articulatory errors such as substitution, omission, addition and distortion errors were still numerous. Compared with those of 0.8 month after onset, omission and substitution errors for consonants 2.8 months after onset decreased, while distortion errors for consonants increased. Substitution and distortion errors for vowels decreased. His speech showed prosodic abnormalities, such as the slow speaking rate resulting from a prolongation of sounds and inappropriate intersyllabic pauses, and monotonous pitch. These disturbances were observed not only in spontaneous speech but also in repetition and reading aloud. Syntax was normal. He had no response to 1 out of 20 objects in the naming task and had articulatory errors to 14 of these objects.

On the other hand, he had perfect scores for auditory comprehension of sentences and of oral

sequential commands. He had no errors for reading comprehension at the two to four-sentence level or for executing written commands that included complicated commands such as 'Pick up the pencil, knock 3 times and put it back.' His written description for a presented picture was adequate and accurate using 3 sentences within 3 min. In the Token Test 2 months after onset the patient performed perfectly. Since his disturbance was limited to oral expression with auditory and reading comprehension and intact writing ability, he was diagnosed as having aphemia. His disturbance at the 2.8 months stage where most of Japanese phonemes appeared in his utterance constituted a pure form of apraxia of speech. His apraxia of speech was still observed 2 yrs after onset, though it had been moderately alleviated.

*Praxis and gnosis testing.* At 0.8 month after onset, he performed perfectly the drawing, block design and praxis subtests of the WAB. There were no indications of constructional, ideomotor or ideational apraxia. He correctly performed the 5 items of the orofacial region in the praxis subtest and the other oral commands such as 'Swallow', 'Puff out your cheeks' and 'Make your teeth chatter'. In contrast, he had some difficulty in executing the commands 'Cough' and 'Click your tongue', indicating a mild orofacial apraxia. At 2.8 months after onset, he perfectly performed the latter two commands. He did not show unilateral hemineglect in drawing pictures. Other apraxias or agnosias were not observed.

*Intelligence testing.* One month after onset, he attained a verbal IQ of 74 and a performance IQ of 85 on the Wechsler Adult Intelligence Scale. His best performance was on the block design subtest (scaled score: 14).

#### Case 2 (T. I.)

A 58-yr-old right-handed man, a middle school graduate, suddenly suffered from weakness and numbness on the right side of his body and speech disturbance on January 4, 1984. He was right-handed, as were his parents, 5 siblings and 2 children. He had been hypertensive for 20 yrs.

Neurological examination 1 month after onset showed right-sided lower facial weakness, deviation of the tongue to the right, a right hemiparesis predominantly affecting the right arm, and right hypaesthesia. The plantar response was extensor on the right. Neurological examination was otherwise negative. A gag reflex was present and there was no difficulty in swallowing. The visual fields were normal. The right hypaesthesia cleared by 2 months after onset. Fibrescope examination revealed that movements of the larynx and pharynx were normal. Six months after onset, neurological examination showed mild right-sided lower facial weakness and a mild right hemiparesis predominantly affecting the right arm. The plantar response remained extensor on the right. Sensory function and the visual fields were normal. Deviation of the tongue was no longer present. Pure tone audiometry and speech audiometry with the 67-A list were within the normal range.

CT scans 1 month after onset and MRI 1 yr after onset showed an infarct mainly affecting the left precentral and postcentral gyri and their underlying deep white matter, such as the middle region of the corona radiata and the left arcuate fasciculus. The left insula was also involved (fig. 2).

*Language testing.* For 1.3 months after onset, spontaneous speech was effortful and slow and consisted of only 1 to 3 syllables. It was limited to /a/, /i/, /o/, /N/, /aʃi/ (foot) and /ohajo:/(good morning). The patient was unable even to say his name.

The WAB was carried out 1.3 months after onset (Table 1). The patient was able to utter only 1 or 2 /N/ to each of the 7 questions in the spontaneous speech task. In the naming task, he had no responses to any of the 20 objects. When the initial syllable of the names were given as cues, he said /boi/ for /bo:l/ (ball) and /maio/ for /naiΦu/ (knife). In the repetition task, substitution, omission and distortion errors were observed. For example he said /ahaha/ for /banana/ (banana). He uttered only 6 different phonemes. The phoneme /n/ occurred four times in his utterances and was articulated correctly once and variously misarticulated three times. There were few self-corrections in his utterances.

He also showed a severe disturbance for reading aloud. On the other hand, auditory comprehension



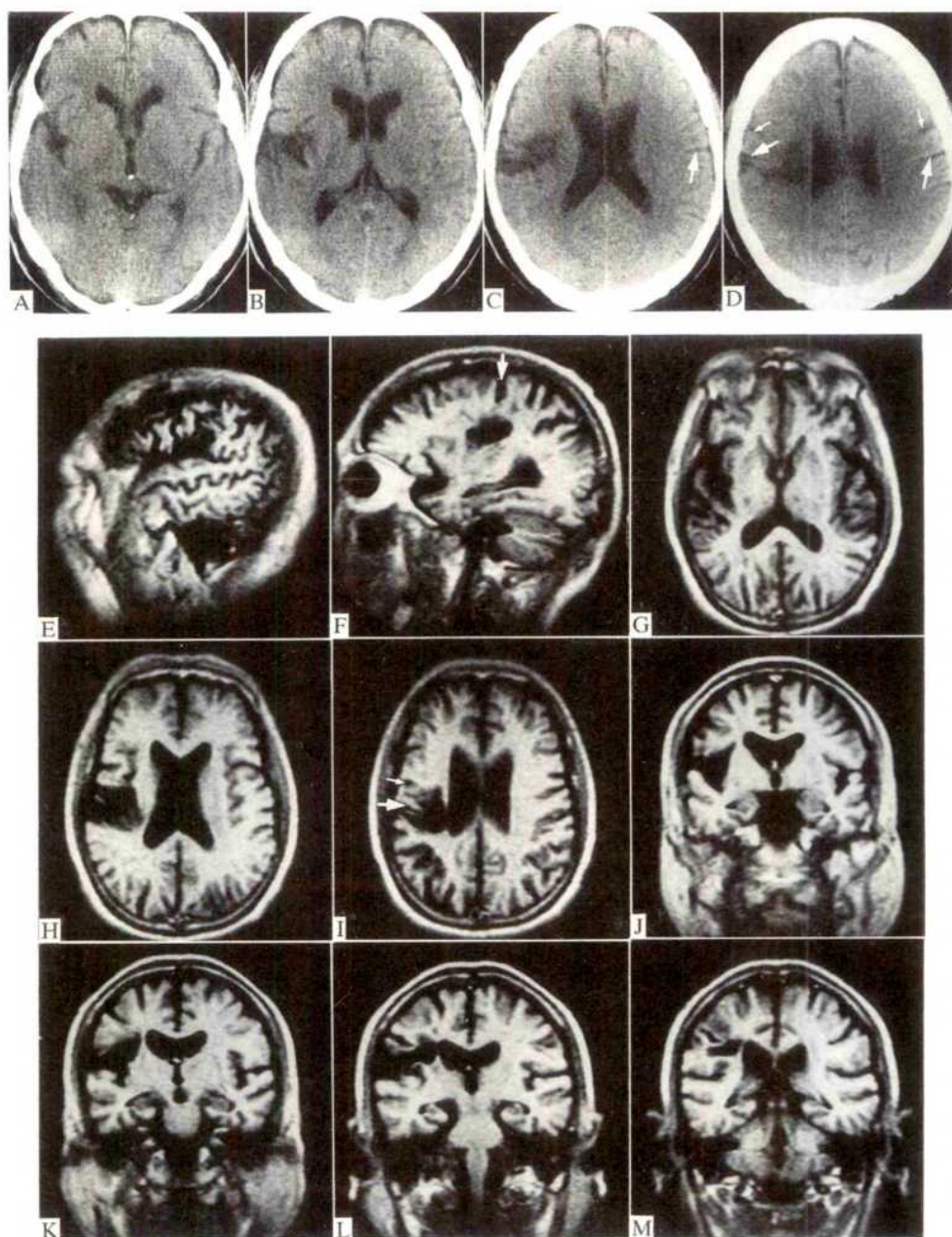


FIG. 2. A-D, CT scans from *Case 2*, 1 month after onset demonstrating an abnormal low density area in the lower parts of the left precentral and postcentral gyri extending deeply into the middle region of the corona radiata. The left arcuate fasciculus and the left insula were also affected. E-M, MRI from this case 1 year after onset revealing an abnormal low intensity area in almost the same area of the left hemisphere. Left central sulcus (large arrows); left precentral sulcus (small arrows).



was well preserved. He responded correctly by gesture to 19 out of 20 'Yes-No' questions and understood and performed correctly all 11 oral sequential commands. In the reading comprehension task, he executed correctly all of the 6 written commands, although he erred on 2 out of the 8 questions which required comprehension of a paragraph. When asked to write a description of a picture, he wrote only 9 nouns with no sentences. His written naming of a stamp, a watch, a pencil and woollen yarn was correct in ideograms (kanji), but showed a mild disturbance in phonograms (kana). However, there was a striking discrepancy between his writing disturbance and that of his speech. In summary, the patient showed severe speech disturbance and mild disturbances in writing and in reading comprehension 1.3 months after onset.

The WAB was readministered 9.6 months after onset. He made no errors in reading comprehension task or dictation of words such as stamp and woollen yarn (Table 1). In the written description of a presented picture he wrote 2 correct sentences having a total of 22 words in 3 min with 2 minor mistakes. He made no errors in writing 25 phonograms. He had perfect scores in the auditory comprehension task and in sequential commands. On the other hand, his speech disturbance was severe. Spontaneous speech and oral repetition was severely hampered by substitution, omission, distortion and addition of sounds, although he had improved to the extent that he often uttered short sentences. In the oral repetition task, omission errors for consonants 9.6 months after onset had decreased compared with the result 1.3 months after onset. Substitution and distortion errors for vowels also decreased. Abnormal prosody characterized by a prolongation of sounds, syllabification and monotonous pitch was apparent. In the naming task, he had no response to 1 out of 20 objects and had articulatory errors to 19 objects. Syntax was within normal limits.

In the Token Test during the same period, the patient had errors on only 2 items in Section F. In summary, his deficits, characterized by isolated severe speech disturbance, was classified as aphemia. His disturbance at the 9.6 month stage, when most phonemes appeared in his speech, constituted an apraxia of speech. The WAB was also tested at 5.3 months after onset in addition to 1.3 months and 9.6 months after onset. The results obtained were very close to those at 9.6 months after onset except that he wrote only one sentence plus 1 word within 3 min in the written description of a picture. His disturbance at this stage is adequately termed a pure apraxia of speech. His apraxia of speech was still present 2 yrs after onset.

*Praxis and gnosis testing.* At both 1.3 months and 9.6 months after onset, he performed the drawing, block design and praxis subtests in the WAB perfectly, which suggested that he did not have constructional, ideomotor or ideational apraxias. One month and 2 months after onset, he correctly performed commands such as 'Open your mouth' and 'Stick out your tongue.' However, he could not 'Cough' or 'Click his tongue', which suggested a mild orofacial apraxia. These two commands were correctly carried out 6 months after onset. Unilateral hemineglect was not observed when drawing pictures. Other apraxias or agnosias were not observed.

*Intelligence testing.* He attained a performance IQ of 105 and a verbal IQ of 81, aided by writing, 1.3 months after onset. Five and a half months after onset, his verbal IQ was 96, and his performance IQ was 104.

## EXPERIMENTAL INVESTIGATIONS

Three articulation tests were employed to obtain speech samples of the 2 patients. Auditory phonetic analysis and electropalatography were used to analyse the speech samples.

### *Articulation*

Three articulation tests were administered to assess the speech disturbance of the 2 patients. One was the Articulation Test developed by the National Rehabilitation Center for the Disabled (ATNR). The second test, the Articulation Test of the Tokyo Metropolitan Institute for Neurosciences (ATTM), had been used for patients before the ATNR was adopted. Most of the test items of the

ATTM were included in the ATNR. The third was a 100-syllable repetition test. The three tests will be briefly described.

*The ATNR.* This test included 82 common nouns of from 2 to 6 syllables in length such as dog, glasses and newspaper. It was administered both as a naming task and for oral repetition. In the naming mode, 82 pictures representing the 82 words were presented, and the patient was asked to name each of them three times successively. In the oral repetition mode, the patient repeated each word three times after the examiner had pronounced it once.

Japanese is an open-syllable language. That is, syllables consist of one consonant and one vowel with or without an intervening /j/ after the consonant. The syllable can, however, be closed with the nasal sound /N/. Therefore there are no final consonants except for /N/ in syllables. /N/ is a unique phoneme which is realized as [m, n, N] and the nasalization of the previous vowel. In this paper, therefore, /N/ was excluded from the analyses.

The total number of phonemes in the 246 responses (82 words  $\times$  3) was 1176, with 537 consonants excluding /N/, 615 vowels and 24 consonant-semivowel clusters. The total numbers of initial consonants and medial consonants in test words were 210 and 327, respectively. All of the Japanese consonants (21 in number): /p, t, k, s, ʃ, Φ, ç, h, b, d, g, ts, tʃ, r, m, n, ɲ, dz, dʒ, j, w/ were tested both in initial and medial positions in words. Four consonant-semivowel clusters, /kj/, /bj/, /gj/, and /rj/, appeared 15 times in initial positions in words, and 3 consonant-semivowel clusters, /pj/, /bj/, and /gj/, appeared 9 times in noninitial positions. All of the Japanese vowels (5 in number): /a, o, e, u, i/ were tested in initial, medial and final positions. The number of vowels tested was 615 (21 initial, 399 medial and 195 final vowels).

*The ATTM.* This test consisted of 32 common words with 2 to 5 syllables. The consonants involved included all of those in the ATNR except for /tʃ, ɲ, dz/. The number of phonemes in the 32 words, excluding /N/, was 163. The patient was asked to name each word 3 times, so that the total number of phonemes tested was 489 (163  $\times$  3). The number of consonants was 225 (81 initial and 144 medial consonants) and the number of vowels 255 (9 initial, 153 medial and 93 final). The number of consonant-semivowel clusters was 9. This test was administered only to Case 2 and only in the naming mode.

*The 100-syllable repetition test.* This test consisted of 100 monosyllables which included all of the possible syllabic combinations of Japanese phonemes. The patient was asked to repeat each syllable twice in succession.

#### *Auditory phonetic analysis*

The responses of the patients were recorded with a cassette tape recorder (Sony TC-D5M) and narrow phonetic transcription using the International Phonetic Alphabet was carried out. The error responses were categorized into two types according to Trost and Canter (1974): inadequate responses and phoneme errors. Inadequate responses included (1) random phonemes, where phoneme strings failed to yield any kind of word approximation; (2) perseverative responses; (3) paraphasic responses, a semantic substitution such as 'hat' for 'coat'; (4) recurrent utterances; and (5) no response (in this study, naming difficulty). Phoneme errors were those responses which were close to the target word but had some errors in terms of phonemes. The phoneme errors were divided into the following four types of errors: (1) substitutions, as in /t/ for /p/; (2) omissions, as in /a/ for /na/; (3) additions, as in /to/ for /o/; and (4) distortions as in /ð/ for /d/. Compound errors, such as distorted substitution or distorted addition errors, were categorized as substitution or addition errors, respectively. The occurrence of sequential errors and self-corrections were also analysed separately. Sequential errors included anticipatory errors such as 'to:to' for 'no:to' (note book), perseverative errors like 'memane' for 'megane' (glasses) and metathetic errors like 'tsukwu' for 'kuwtsu' (shoes).

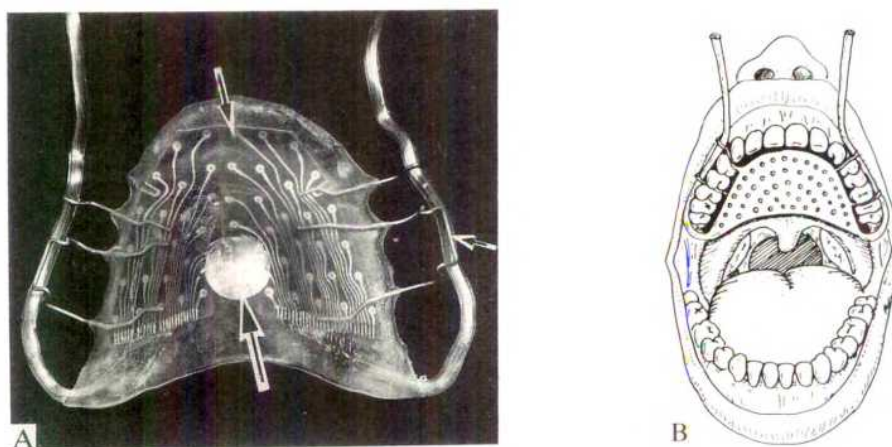


FIG. 3. Artificial palate. A, photograph of an artificial palate. Receiving electrode (large arrow); one of the transmission electrodes (middle-sized arrow); lead wire (small arrow). B, artificial palate fitted against the patient's palate.

#### *Electropalatography*

Electropalatography (Rion Co. Ltd) was employed to observe the palatolingual contact during the entire ATNR and ATTM naming tests. The system of electropalatography used in this study included an artificial palate, a display panel with a memory system, a recording adapter connected to a dual-channel tape recorder (Sony TC-D5M) and a graphic printer. The artificial palate made of transparent plastic (1 mm in thickness) was formed after a plaster model of the palate of each patient. It had 63 gold transmission electrodes (2 mm diameter each) implanted on its under surface and 1 gold receiving electrode (8 mm diameter) on the upper surface (fig. 3A). The output from a signal source was applied to each transmission electrode through a distributor controlled synchronously by a clock oscillator. The artificial palate was fitted against the patient's hard palate (fig. 3B). When the tongue touched the transmission electrodes the current ran to the receiving electrode and was sensed by detectors. The signals were then transmitted to the memory system which processed the signals at a rate of 64 frames/s; 63 light emission diodes on a display panel showed the positions of the electrodes which the tongue touched. Both the signals and speech were stored on a dual-channel cassette tape via a recording adaptor. The data on the cassette tape could be reproduced and observed in slow motion on the display panel (fig. 4).

The patterns of the palatolingual contacts for the 2 patients were then printed out and compared with those of 5 normal subjects who spoke each word 3 times, giving 15 normal patterns. The data for omission errors were classified into three types of palatolingual contact: correct contact, incorrect contact and no contact. The palatolingual contact patterns of the phonemes omitted by the patients were judged correct when they did not exceed the maximum or minimum contact range of the normal patterns of target sounds. They were judged incorrect when they were within the maximum or minimum contact range of different sounds or they were undifferentiated contact patterns, that is, exceeding the maximum or minimum contact range of any sound. They were judged no contact when they had no palatolingual contact.

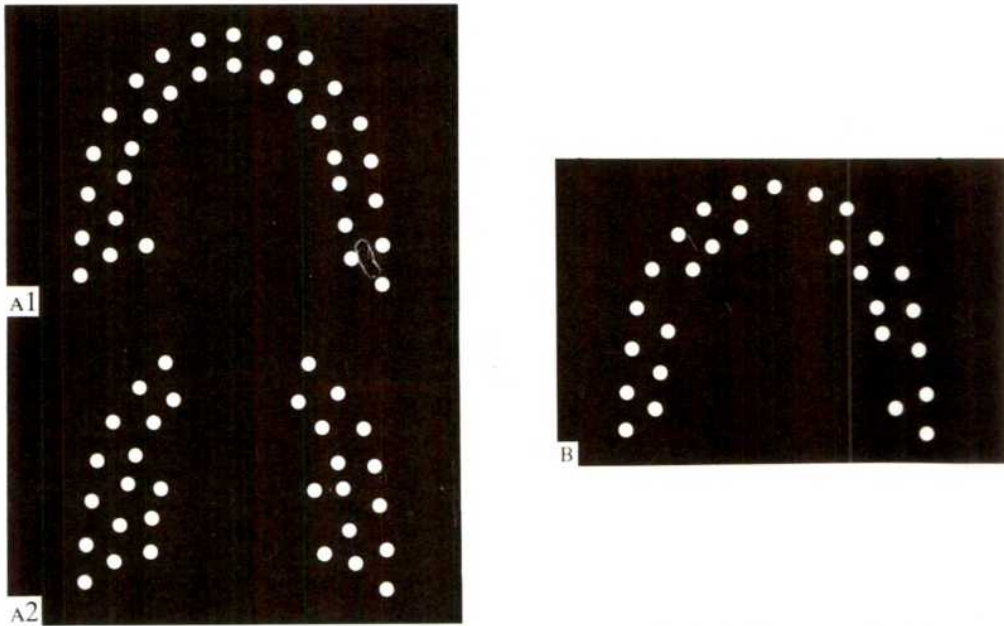


FIG. 4. Electropalatograms from *Case 1* shown on the display panel. Transmission electrodes in contact with the tongue are indicated by the light emission diodes of the display panel which are small circles in the electropalatograms. A1, A2, correct contact of palatolingual pattern for the target sound /dʒ/ A1 is its closure and A2 is its release following closure. B, substituted pattern of palatolingual contact for the target sound /j/ to lingual-alveolar sounds such as /t/, /d/ or /n/. Both (A, B) were perceived as omission errors.

## RESULTS

### *Case 1*

#### *Auditory phonetic analysis*

*ATNR naming test.* This test was carried out in the naming mode 2.3 months after onset. Out of the 82 test words, 2 (pencil and telephone) were not tested. The 80 pictures representing the 80 words were named 3 times, so that the patient produced 240 responses (80 words  $\times$  3) on which auditory phonetic analysis was performed.

Out of the 240 responses, 55 responses were correct and 185 responses were judged as having phoneme errors. There were no inadequate responses such as no responses (naming difficulties). The 185 phoneme-error responses had 290 erroneous phonemes, that is, 25% of the total number of phonemes (1149). The phoneme errors included 63% (182/290) substitution errors, 22% (64/290) omission errors, 14% (41/290) distortion errors and 1% (3/290) addition errors. There were no omission or addition errors of syllable units. Self-correction responses were only 2% (7/290) of the total errors. Nine sequential errors (8 anticipatory, 1 perseverative) were observed. They accounted for only 3% (9/290) of the total

errors. Further analysis for consonant, consonant-semivowel cluster and vowel errors was as follows.

1. Consonants. The patient made 261 consonant errors, involving 50% (261/525) of the total consonants used in the test (Table 2). There were no significant differences in the numbers and the types of errors between the first, second and third responses. The percentage of errors was 74% (153/207) for initial consonants and 34% (108/318) for medial consonants, indicating that initial consonants elicited more errors than medial consonants ( $\chi^2 = 80.1$ ,  $P < 0.01$ ). Errors were observed for all 21 consonants. The consonant with the lowest percentage of errors was /p/ (17%) followed by /tʃ/ (29%), /m/ (29%), /w/ (33%), /k/ (40%) and /t/ (41%). Those with higher percentages were /dz/ (95%) /ts/ (88%) /s/ (81%) /d/ (73%) and /dʒ/ (73%) (fig. 5). This indicated that the most difficult consonants were affricates and fricatives.

Out of 261 consonant errors, 63% were substitutions, 23% omissions, and 14% distortions, with no errors of addition (Table 2). Substitution errors occurred for all 21 Japanese consonants, and were highly inconsistent. Seventeen consonants which elicited more than 3 substitution errors (i.e., /j, p, t, k, b, d, g, m, n, s, h, ts, dz, r, ʃ, tʃ, dʒ/) were substituted by more than 2 different consonants. These consonants were changed to 18 different consonants (/p, t, k, ʃ, Φ, ç, h, b, d, g, ts, tʃ, r, n, ɲ, dz, dʒ, j/), with substitutions of /t/ (20), /tʃ/ (18), /k/ (14) and /n/ (13) occurring most frequently.

When analysing the consonants for consonant-substitution errors using the four subphonetic dimensions of Trost and Canter (1974) — that is, place, manner, voicing and oral-nasal — 60% (91) were off by one dimension, followed by those off by two dimensions 29% (45), three dimensions 8% (12) and four dimensions 3% (4). Place was the most frequent error, 48% (111), followed by manner errors 26% (59), voicing errors 19% (43) and oral-nasal errors 7% (16). There were more voiceless substitution errors for voiced consonants, 81% (35), than the reverse type of error, 19% (8), indicating a strong tendency toward devoicing.

Sixty omission errors were observed for 17 different consonants among the 21 different test consonants (fig. 5). While the omission error percentages varied from 29% for /dz/ to 6% for /ʃ/ and /j/, there were no significant differences between

TABLE 2. CONSONANT, VOWEL AND CONSONANT-SEMIVOWEL CLUSTER ERRORS, AND EACH TYPE OF ERROR IN CASE 1, 2.3 MONTHS AFTER ONSET\*

|                     | <i>Consonant</i> | <i>Vowel</i> | <i>Consonant-semivowel</i> | <i>Total</i> |
|---------------------|------------------|--------------|----------------------------|--------------|
| Sound tested        | 525              | 600          | 24                         | 1149         |
| Errors (error rate) | 261(50%)         | 17( 3%)      | 12(50%)                    | 290(25%)     |
| Error type          |                  |              |                            |              |
| Substitution        | 165(63%)         | 9(53%)       | 8(67%)                     | 182(63%)     |
| Omission            | 60(23%)          | 0( 0%)       | 4(33%)                     | 64(22%)      |
| Addition            | 0( 0%)           | 3(18%)       | 0( 0%)                     | 3( 1%)       |
| Distortion          | 36(14%)          | 5(29%)       | 0( 0%)                     | 41(14%)      |

\*The ATNR naming test was employed.



2. Vowels. Vowel errors occurred much less often than consonant errors ( $\chi^2 = 330.8$ ,  $P < 0.01$ ), only 3% of the total number of vowels (17/600) (Table 2). These vowel errors occurred most frequently for initial vowels at 22% (4/18), compared with medial vowels at 2% (9/393) and final vowels at 2% (4/189) (Fisher's

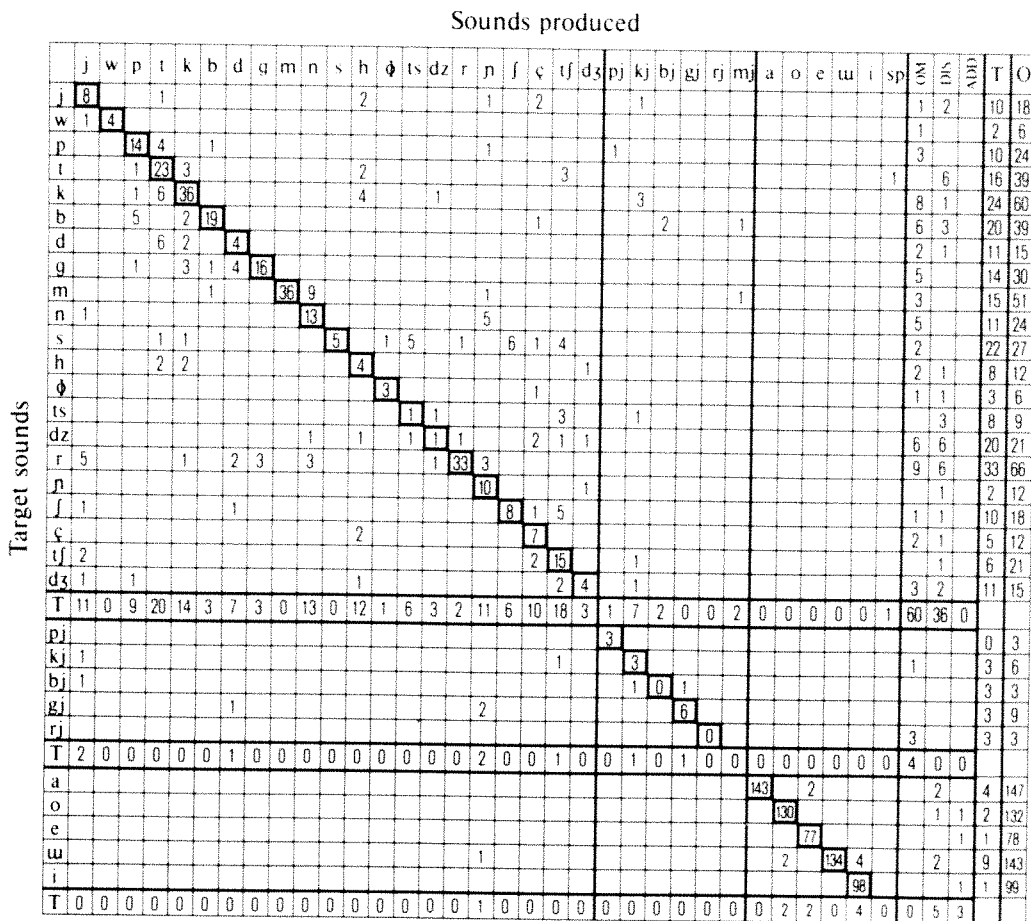


FIG. 5. Confusion matrix of consonants, consonant-semivowel clusters and vowels for *Case 1*, 2.3 months after onset. Each line of the matrix shows the distribution of sounds which the patient produced in response to the target sounds as indicated on the left margin. Cells forming the diagonal are correct productions. SP=sounds not existing in Japanese language but possible to transcribe by International Phonetic Alphabet. OM=omission; DIS=distortion; ADD=addition; T=total number of errors; O=total number of occurrences of each target sound.

exact test,  $P < 0.01$ ). Errors occurred for all 5 vowels. The highest error rate was 6% for /u/ and the lowest was 1% for /i/. Less substitution, omission and addition errors were observed for vowels than for consonants (substitution errors:  $\chi^2 = 191.8$ ,  $P < 0.01$ ; omission errors: Fisher's exact test,  $P < 0.05$ ; distortion errors: Fisher's exact test,  $P < 0.01$ ). Substitution errors accounted for 53% of the total number of vowel errors, followed by distortion errors 29% and addition errors 18%, with no omission errors (Table 2). Eight of the 9 substitution errors were substituted vowels, and only 1 was a consonant.

3. Consonant-semivowel clusters. Out of 24 consonant-semivowel clusters tested, 50% were judged to have errors. The error rate 100% for /bj/ (3/3) and /rj/ (3/3). The lowest error rate was 0% for /pj/ (0/3). Substitution errors were 67%, followed by omission errors at 33%. There were no addition or distortion errors (Table 2).

### *Electropalatographic analysis of omission errors*

In order to clarify the nature of the omission errors, electropalatography was carried out during the entire ATNR naming test, 2.3 months after onset. The phonemes articulated with the tongue against the hard palate in Japanese are 14: /t, d, tʃ, dʒ, ts, dz, ɕ, ʃ, n, ɲ, s, r, j, rj/: 34 of the total of 64 omission errors were for 10 of these 14 phonemes articulated with the tongue against the hard palate and these 34 were submitted to analysis (Table 3). The results revealed palatolingual

TABLE 3. ELECTROPALATOGRAPHIC ANALYSIS OF OMISSION ERRORS IN CASE 1, 2.3 MONTHS AFTER ONSET\*

| Types of palatolingual contact | Target sounds |   |   |   |    |   |   |   |    |    | Total  |
|--------------------------------|---------------|---|---|---|----|---|---|---|----|----|--------|
|                                | j             | d | n | s | dz | r | ʃ | ɕ | dʒ | rj |        |
| Correct contact                | 1             | 2 | 5 |   | 4  | 1 |   | 1 | 1  |    | 15     |
| Incorrect contact              |               |   |   |   |    |   |   |   |    |    |        |
| Different sound                |               |   |   | 1 | 2  | 2 | 0 | 0 | 1  | 3  | 9<br>5 |
| Undifferentiated sound         |               |   |   | 1 |    | 2 | 1 | 1 |    |    |        |
| No contact                     |               |   |   |   |    | 4 |   |   | 1  |    | 5      |

\*Scores indicate occurrence of each type of palatolingual contact.

contact for the target phonemes (correct palatolingual contact) in 15 out of the 34 omission errors, and palatolingual contact for different sounds or undifferentiated sounds (incorrect palatolingual contact) in 14 out of the 34 omission errors. On the other hand, those which showed no palatolingual contact — that is, true omission errors — proved to be only 5 out of the 34 (Table 3). All of the omission errors with correct contact (15/15) and most of the omission errors with incorrect contact (13/14) occurred for initial consonants. On the other hand, more than half of the true omission errors (3/5) were observed for medial consonants.

*Repetition versus naming*

The ATNR was also carried out in the repetition mode 2.3 months after onset. Compared with the result for the naming mode at the same period, no differences were observed either in the error rate or in the distribution of the four types of errors. In the repetition mode, as in the naming mode, no significant differences were found in the rates or types of errors between the first, second and third responses for the test words.

The patient also had great difficulty in doing the 100-syllable repetition test. Sixty-one percent of the phonemes (233/378) were erroneous 0.9 month after onset: consonants 89% (131/148), vowels 36% (70/194), consonant-semivowel clusters 89% (32/36). Four months after onset, the errors had decreased greatly to 27% (106/390): consonants 51% (78/154), vowels 6% (12/200), consonant-semivowel clusters 44% (16/36).

*Case 2**Auditory phonetic analysis*

*ATTM naming test.* The ATTM, consisting of 32 words, was administered in the naming mode 4.5 months after onset. Thirty-two pictures representing the 32 words were named 3 times, so that 96 responses were obtained. The 96 responses included 6 correct responses and 90 responses judged as having phoneme errors. There were no inadequate responses such as no responses (naming difficulties). One self-correction response was observed. The 90 erroneous responses had 156 phoneme errors, or 32% of the total number of phonemes tested (489) (Table 4). Sequential errors were only 8 (3 anticipatory and 5 perseverative). Errors for consonants were 58% (131/225) and for consonant-semivowel clusters 100% (9/9). Vowel errors were only 6% (16/255). Consonant errors were more frequent than vowel errors ( $\chi^2 = 151.8$ ,  $P < 0.01$ ). Consonant-semivowel cluster errors were more frequent than vowel errors ( $\chi^2 = 88.0$ ,  $P < 0.01$ ). More substitution, omission and addition errors were observed on consonants than on vowels (both substitution errors and omission errors: Fisher's exact test,  $P < 0.01$ ; addition errors,  $P < 0.05$ ). For consonants, substitution errors, at 92% of the total errors, were more frequent than the other types of error. The most frequent for vowels were addition errors (56%) and for consonant-semivowel clusters, substitution errors (78%) (Table 5).

*ATNR naming test.* The ATNR, consisting of 82 words, was administered in the naming mode 9.6 months after onset, and 246 responses (82 words  $\times$  3) were obtained. Since the patient had no responses (naming difficulties) to 2 pictures representing 2 words (a colouring book and a penguin), 6 responses (2 words  $\times$  3) were judged as inadequate responses. There were 18 correct responses. The remaining 222 responses were judged as having phoneme errors, and they were submitted for auditory phonetic analysis. There were no self-corrections.

We observed 362 phoneme errors in the 222 responses, or 31% of the total 1149





TABLE 4. CONSONANT, VOWEL AND CONSONANT-SEMIVOWEL CLUSTER ERRORS, AND EACH TYPE OF ERROR IN CASE 2, 4.5 AND 9.6 MONTHS AFTER ONSET

|                        | <i>Consonant</i> | <i>Vowel</i> | <i>Consonant-semivowel</i> | <i>Total</i> |
|------------------------|------------------|--------------|----------------------------|--------------|
| 4.5 months after onset |                  |              |                            |              |
| Sound tested           | 225              | 255          | 9                          | 489          |
| Errors (error rate)    | 131(58%)         | 16(6%)       | 9(100%)                    | 156(32%)     |
| Error type             |                  |              |                            |              |
| Substitution           | 121(92%)         | 4(25%)       | 7(78%)                     | 132(84%)     |
| Omission               | 7(5%)            | 0(0%)        | 0(0%)                      | 7(5%)        |
| Addition               | 1(1%)            | 9(56%)       | 0(0%)                      | 10(6%)       |
| Distortion             | 2(2%)            | 3(19%)       | 2(22%)                     | 7(5%)        |
| 9.6 months after onset |                  |              |                            |              |
| Sound tested           | 525              | 600          | 24                         | 1149         |
| Errors (error rate)    | 301(57%)         | 41(7%)       | 20(83%)                    | 362(31%)     |
| Error type             |                  |              |                            |              |
| Substitution           | 262(87%)         | 0(0%)        | 20(100%)                   | 282(78%)     |
| Omission               | 3(1%)            | 0(0%)        | 0(0%)                      | 3(1%)        |
| Addition               | 0(0%)            | 30(73%)      | 0(0%)                      | 30(8%)       |
| Distortion             | 36(12%)          | 11(27%)      | 0(0%)                      | 47(13%)      |

\*The ATTM naming test was employed 4.5 months after onset, and the ATNR naming test 9.6 months after onset.

indicating more errors for initial consonants than for medial ones ( $\chi^2 = 72.5$ ,  $P < 0.01$ ). Errors were observed for all of the 20 consonants except for /*n*/. The error rate was the highest for /*g*/ (27/27) and /*ʃ*/ (6/6) at 100%, followed by /*ç*/ (92%), /*dz*/ (90%), /*f*/ (89%) and /*s*/ (81%), again indicating that the most difficult sounds were fricatives and affricates. The lowest was 0% for /*n*/ (0/12), followed by /*tʃ*/ (14%), /*t*/ (26%), and /*m*/ (29%) (fig. 6). Substitution errors were the most common at 87% (262), followed by distortion errors at 12% (36) and omission errors at 1% (3), with no addition errors.

The substitution errors were inconsistent. Most of the consonants — excluding /*n*/ of no errors and /*ts*/, all of whose substitution errors were to /*tʃ*/ — were substituted for by more than 2 different consonants. Although the direction of the substitution was not consistent, there was a striking tendency for most of the consonants to be substituted for by /*t*/ 26% (68), or /*tʃ*/ 24% (61).

When analysing the consonant-for-consonant substitution errors under the four dimensions proposed by Trost and Canter (1974), most of the errors differed by one dimension 50% (126) or two dimensions 46% (115) from the target, followed by three dimensions 4% (9). Place errors accounted for 46% (175), followed by manner errors at 35% (132), voicing errors at 15% (58) and oral-nasal errors at 4% (16). There was a striking tendency toward devoicing. The patient made more voiceless substitution errors 88% (51) for voiced consonants than the reverse type of error 12% (7).

A total of 3 omission errors was observed for 2 different consonants. Thirty-six distortion errors, which were observed for 9 different consonants, including palatalization 17% (6), partial devoicing 11% (4), partial omission of sounds 3% (1) and others 69% (25).

2. Vowels. Forty-one vowel errors were observed, that is, in 7% of the vowels

tested (41/600). This was much lower than the error rate for consonants ( $\chi^2 = 337.5$ ,  $P < 0.01$ ). These vowel errors occurred most frequently for initial vowels at 90% (19/21), followed by errors for medial ones at 6% (22/387), with no errors for final vowels (0/192) (Fisher's exact test,  $P < 0.01$ ). Errors occurred to all of the 5 vowels. The error rate was the highest for /e/ (9/78) at 12%. The lowest was 3% for /u/ (5/144). Less substitution, addition and distortion errors were observed on vowels than on consonants (Fisher's exact test,  $P < 0.01$ ). Addition errors accounted for 73% of the total number of vowel errors, followed by distortion errors at 27%, while no substitution or omission errors were observed (Table 4). Most of the addition errors occurred for initial vowels. The frequent phonemes added were /t/ (8), /b/ (5), /d/ (4), /dʒ/ (3) and /j/ (3).

3. Consonant-semivowel clusters. The consonant-semivowel clusters having errors numbered 20 (83%) out of the 24 consonant-semivowel clusters tested (Table 4). The error rate was 100% for /kj/ (6/6), /pj/ (3/3) and /bj/ (3/3). The lowest error rate was 0% (0/3) for /rj/. All of these 20 errors were substitution errors.

#### *Electropalatographic analysis of the omission errors*

Electropalatography was conducted during the entire ATTM naming test 4.5 months after onset. The results included 7 omission errors for consonants. Six of these were phonemes articulated with the tongue against the hard palate. They were submitted to analysis. The result showed 1 omission error with correct palatolingual contact, 2 with incorrect palatolingual contact and 3 with no palatolingual contact (Table 5). All the omission errors with correct contact and with incorrect contact occurred for initial consonants, while all the errors with no contact — that is, true omission errors — were observed for medial consonants.

At the stage of 9.6 months after onset, electropalatography was conducted during the entire ATNR naming test. The results showed 3 omission errors for consonants. The electropalatography showed correct contact in one of the 3 omission errors and no contact in the remaining 2 omission errors, indicating true omissions (Table

TABLE 5. ELECTROPALATOGRAPHIC ANALYSIS OF OMISSION ERRORS IN CASE 2\*

| Types of palatolingual contact | Interval postonset tested  |          |           |          |          |                            |          | Total |
|--------------------------------|----------------------------|----------|-----------|----------|----------|----------------------------|----------|-------|
|                                | 4.5 months<br>Target sound |          |           |          |          | 9.6 months<br>Target sound |          |       |
|                                | <i>j</i>                   | <i>d</i> | <i>dʒ</i> | <i>r</i> | <i>t</i> | <i>r</i>                   | <i>m</i> |       |
| Correct contact                |                            |          |           |          | 1        |                            | 1        | 2     |
| Incorrect contact              |                            |          |           |          |          |                            |          |       |
| Different sound                |                            | 1        |           |          |          |                            |          | 1 } 2 |
| Undifferentiated sound         |                            |          | 1         |          |          |                            |          | 1 }   |
| No contact                     | 1                          |          |           | 2        |          | 2                          |          | 5     |

\*Scores indicate occurrence of each type of palatolingual contact.

5). The omission error with correct contact was again observed for initial consonant and those with no contact were for medial consonants.

### *Repetition versus naming*

The ATNR in the repetition mode was given to the patient 5 months after onset. Compared with the result for the naming mode at the same period, no differences were observed, either in the errors rate or in the distribution of the four types of errors. There were no differences in the rates or types of errors between the first, second and third responses for each word, as in the naming mode.

In the 100-syllable repetition test 1.5 months after onset, the patient produced errors for 324 (85%) out of the 382 phonemes tested: consonants 91% (137/150), vowels 77% (151/196) and consonant-semivowel clusters 100% (36/36). At 8.5 months after onset, the number of errors decreased to 47% (184/390): consonants 73% (112/154), vowels 20% (39/200) and consonant-semivowel clusters 92% (33/36).

## DISCUSSION

Our 2 patients, a left-hander with a right hemisphere lesion and a right-hander with a left hemisphere lesion had disturbances limited to speech output, while their auditory and reading comprehension as well as writing remained nearly normal. During the early period following onset, the patients were able to articulate only very limited sounds. Several months following onset, the patients recovered enough to articulate most of the Japanese phonemes, but showed many inconsistent substitution, omission, distortion and addition errors. The disturbance at this stage is well covered by the term 'apraxia of speech' (F. L. Darley, unpublished).

At this stage, the patients had almost no naming difficulties in the naming task of the WAB, the ATTM or ATNR naming test. They pronounced an approximation of each target word in the naming tests. Furthermore, they were able to write the words correctly. These findings suggest that their disturbance was not a naming (word finding) difficulty but an articulatory disturbance.

The articulatory characteristics of apraxia of speech are still controversial in many respects (Wertz *et al.*, 1984). Almost all phonetic studies of apraxia of speech have been based on cases with apraxia of speech associated with aphasia (Shankweiler and Harris, 1966; Johns and Darley, 1970; Trost and Canter, 1974; LaPointe and Johns, 1975). The discrepancies among these findings had probably been caused by differences both in severity and in the type of aphasia accompanying apraxia of speech. There are a few accounts (Sasanuma, 1971; Lecours and Lhermitte, 1976; Square *et al.*, 1981) of phonetically studied cases with apraxia of speech not complicated by aphasia, but these have been preliminary reports and mutually contradictory. More detailed articulation studies of apraxia of speech uncontaminated with aphasia are necessary to clarify the details of the syndrome of apraxia of speech. Since our cases had apraxia of speech not accompanied by aphasia, it is worthwhile to describe their articulatory characteristics.

*Articulatory characteristics on auditory phonetic analysis*

Although the side of the lesion and the handedness of the 2 cases were different, their articulatory characteristics were almost the same. The systematic phonetic analysis of speech production in the 2 patients several months after onset, when they exhibited a typical apraxia of speech, showed the following 15 common characteristics. (1) Errors occurred for almost all phonemes. There was only one phoneme (/p/ in Case 2) which were always correct among the phonemes tested more than 4 times. (2) Two types of inconsistency were observed in their errors: a phoneme was incorrect at one time but correctly articulated at another; errors for the same phoneme differed from time to time. These two types of inconsistency have been emphasized as an important characteristic of apraxia of speech in contrast to dysarthria arising from damage to the bilateral corticobulbar tracts, the cerebellum or the lower motor neuron, where errors are consistent. However, there was one exception (/g/ in Case 2) to the first type of inconsistency. On the other hand, there was no exception to the second type of inconsistency among the phonemes tested more than 3 times. Even the phoneme /g/ in Case 1 showed the second type of inconsistency.

The following three conditions (3, 4, 5) elicited more errors. (3) Errors occurred more frequently on consonants than on vowels. (4) The most difficult consonants were affricates and fricatives. More substitution, distortion and omission errors were observed on consonants than on vowels. (5) More errors were made for initial sounds than for noninitial sounds, even when repetitions and retrials were excluded.

(6) The tendency in error types was for substitution errors for consonants to be more frequent than omission, distortion or addition errors, both in naming and in oral repetition of words. However, in the single-syllable repetition of Case 1, omission errors exceeded substitution errors.

The following five characteristics (7, 8, 9, 10, 11) on their substitution errors were revealed. (7) There was a tendency to substitute 1 of the 2 consonants /t, tʃ/ for other sounds. This characteristic is quite important for speculation on the nature of apraxia of speech. It suggests that the patients had difficulty in preventing the tip of the tongue from rising up to the alveolar and postalveolar region. Therefore apraxia of speech may involve problems with inhibition of tongue activity. (8) Consonants were seldom substituted for vowels, or vice versa (9) Over half the substitution error sounds were different from the target by one phonetic dimension, and over 90% of the errors were limited to one or two dimensions, using the scale of Trost and Canter (1974). The two characteristics (8) and (9) indicate that the substituted sounds were relatively close to the target sounds. (10) Substitution errors were most likely to involve errors of place, followed in order by errors of manner, voicing and the oral-nasal distinction. (11) Voiceless-for-voiced substitutions were more frequent than voiced-for-voiceless substitution.

The sequential errors and self-corrections, although they were often discussed in the previous literature, were relatively small in number ((12) and (13)). (12) The

percentage of sequential errors — that is, anticipatory, perseveratory and metathetic errors — relative to the total number of errors was low (less than 10%). (13) The number of self-corrections was small in our 2 patients (less than 2%). Some researchers (e.g., Darley, 1982; Wertz *et al.*, 1984) have suggested self-correction as one of the main characteristics of 'apraxia of speech'. However, when they knew that they had made some errors anyway, our 2 patients gave up self-correction and chose to continue their utterances of communicative efficiency without self-correction.

(14) Spontaneous speech (naming) accuracy was not better than oral repetition accuracy. (15) No significant differences in accuracy were observed between the first, second and third response either in the naming or in the oral repetition mode. This characteristic was observed both for initial sounds and for noninitial sounds.

There were a few differences in the disturbance between our 2 cases: omission errors were observed more in Case 1 than in Case 2 (Fisher's exact test,  $P < 0.01$ ); addition errors were more in Case 2 than in Case 1 (Fisher's exact test,  $P < 0.01$ ). Further studies are needed to establish whether these differences are due to differences in their lesions or individual factors.

As well as at the later stage described above, at the very early stage when their articulation was limited to 6 to 9 different sounds, substitution, omission and distortion errors were observed although they were small in number. Phonemes which occurred more than twice were articulated incorrectly at one time but correctly at others. The nature of the errors seems very similar to those of the later stage.

#### *Omission errors*

Our electropalatographic results revealed that what were categorized auditorily as omission errors could be classified into three types: omission errors with no palatolingual contact (true omissions); omission errors with incorrect palatolingual contact (palatolingual contact exists but it is for different sounds or for undifferentiated sounds which therefore would be a substitution error or a distortion error with air flow); and omission errors with correct palatolingual contact (palatolingual contact for the target sound exists and would be realized as the correct sound with air flow). Almost all omission errors with correct or incorrect contact were observed for initial consonants, which is important for inferring the causes of this type of omission error as will be discussed below.

Darley (1982) considered omission errors as errors of simplification and thus not characteristic of apraxia of speech. However, our results from electropalatography go against this hypothesis by revealing the existence of omission errors with incorrect contact, which are thus not errors of simplification.

The omission errors with correct or incorrect contact were probably caused by a delay in air flow for the following three reasons. First, they had palatolingual contact. Secondly, almost all omission errors with correct or incorrect contact occurred at the beginning of utterances, that is, for initial consonants. Thirdly, the

distortion errors in our patients included partial omission errors, where a weak and short sound was perceived. These were probably due to a slight delay in air flow.

A delay in air flow also may explain why vowels elicited less omission errors than consonants (*see* Characteristic 3). Air flow almost always starts during a consonant before a vowel. Consequently a delay in air flow occurred less frequently during a vowel.

### *Apraxia*

Is the syndrome 'apraxia of speech' really apraxia? Apraxia was defined by Liepmann (1900) as follows: 'Apraxia is, in short, the inability to act, i.e., to move the moveable parts of the body as intended, though motility is preserved. The notion of falsity, unfitness for the purpose, is conveyed by the word "apraxia"'. The motility of the articulatory apparatus of our 2 patients was preserved, since they had neither significant paresis, ataxia nor involuntary movement, and since they articulated correctly target sounds at one time but not at others. Their articulatory errors — such as substitution, omissions, distortions and addition errors — were not their intended responses, which was verified by the fact that they were able to write the target words correctly. Therefore the speech disturbance of our 2 cases seems to be apraxia. The term 'apraxia of speech' can be employed for 'pure' apraxia of speech such as that shown by our cases but not for apraxia of speech complicated with aphasia, where the intention of patients cannot be checked in writing (Sugishita, 1981).

Liepmann (1920) classified apraxia into three types: limb-kinetic, ideomotor and ideational apraxia. The apraxias concern limbs and face movements but do not concern articulatory movements. Though Liepmann mentioned that speech disturbance of expressive aphasia (probably apraxia of speech plus aphasia) was apraxia, he did not specify into which type of apraxia the speech disturbance was classified. Liepmann (1920) described substitution errors of the limbs as errors of ideomotor apraxia, and omission errors as those of ideational apraxia. Limb-kinetic apraxia, defined as a loss of skill in learned movements and inability to form the beginning of movements, may be applicable to distortion errors and null responses. Our patients often had a substitution error on a phoneme but had a distortion, omission or addition error on the same phoneme at other times. Consequently, none of the three types of apraxia seems to fit apraxia of speech.

Many studies (Nathan, 1947; Denny-Brown, 1965; Tonkonogy and Goodglass, 1985) observed that apraxia of speech and oral apraxia coexist, while there were a few cases with apraxia of speech and no oral apraxia (Lebrun *et al.*, 1973). Denny-Brown (1965) observed that there were certain tasks, such as cough or whistle, which are very sensitive to even mild oral apraxia. Both of our 2 patients showed a slight oral apraxia at the early stage: they could not cough and click their tongue. The results suggest that apraxia of speech and oral apraxia coexist early after onset.

The reported cases with apraxia of speech having no oral apraxia had probably been tested without the sensitive tasks.

### *Localization of the lesion causing apraxia of speech*

Lecours and Lhermitte (1976) have indicated that a corticosubcortical lesion in the lower part of the left precentral gyrus causes pure anarthria (apraxia of speech) in the right-handed. Tonkonogy and Goodglass (1981) have argued that a lesion in the lower parts of the precentral and postcentral gyri causes aphemia (apraxia of speech) in the right-handed. These hypotheses are consistent with the lesion of our second patient who was right-handed, although his lesion extended deeply into the white matter underlying the precentral and postcentral gyri, making his syndrome severe.

A left-handed patient with apraxia of speech has not been reported as far as we know. It would be interesting to know in which hemisphere the lesion in such a patient is sited and whether it is focal or diffuse. Most left-handed aphasics have left hemisphere damage, the remainder having right hemisphere damage (Hécaen and Sauguët, 1971). The first case in this study, who was a nonfamilial left-hander, had a focal lesion in the right hemisphere, namely, a corticosubcortical lesion mainly affecting the lower part of the right precentral gyrus and its underlying deep white matter. This finding suggests that, in some left-handers, speech is unilaterally and focally represented in a manner opposite to that of most right-handers, that is, in the right hemisphere. Our first case is therefore not consistent with the hypothesis of Hécaen *et al.* (1981) that, for left-handers, speech is represented in the left hemisphere or bilaterally. Our finding suggests that, in non-familial left-handers, speech is unilaterally and focally represented in the right hemisphere, as proposed by Delis *et al.* (1983).

Our results indicate two possible components of apraxia of speech: one is a delay in air flow, and the other is difficulty in the inhibition of tongue activity. Furthermore, both of these do not always occur, and this inconsistency could be a common characteristic of these disturbances. To clarify the nature of apraxia of speech, further studies of apraxia of speech uncomplicated by aphasia as in our cases will be indispensable.

### ACKNOWLEDGEMENTS

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## BOOK REVIEWS

**Neurological Assessment During the First Year of Life.** By C. Amiel-Tison and A. Grenier. 1986. Pp. 197. New York and Oxford: Oxford University Press. Price £30.00.

Neonatal neurology has deep roots in France dating back to 1944, when the late André-Thomas, after many years as a general neurologist, became interested in the neurology of the newborn infant and resolved to dedicate his remaining years to the problems of this age group. With his colleague, Saint-Anne Dargassies at the Clinique Baudelocque in Paris, he developed specialized techniques of neurological examination of the newborn and built up a large corpus of knowledge of the normal and abnormal in this most interesting, but previously rather neglected, field. The Paris school have shown the neurological maturation of the prematurely born infant as he approaches his expected date of delivery, defining criteria to which he conforms at certain stages of maturation. These stages in early 'developmental neurology' lead, in healthy infants, to a situation at term similar to that of the baby delivered at term after spending the appointed 40 weeks in his mother's womb. Thus the neurological examination allows an assessment of neurological maturity and hence of gestational age in the premature infant as well as the detection of anomalies which may have significance for the functional integrity of the nervous system and for the future development of the child. With obstetric and paediatric advances which have led to the survival of increasing numbers of prematurely born infants, these methods have assumed greater importance in recent years.

There have been previous publications from the Paris school, mostly in French, but the work is not as well known elsewhere as it deserves to be. In part this may be due to differences in terminology, relating especially to the concept of 'tonus', which is far more complex and rewarding for French and other European neurologists than is the word 'tone' as used by most Anglophone physicians. The exploration of tonus includes both active and passive aspects. Active tonus comprises, and indeed determines, the posture at rest and spontaneous and provoked movement of the infant. Passive tonus has three aspects. Extensibilité indicates the lengthening capacity of limb muscles as shown by the range through which certain joints can be passively moved. This is the aspect of tone most often assessed in conventional neurology, but the observations are made at many more joints, at the wrist (window sign), elbow or shoulder (signe de foulard or scarf sign), knee (popliteal angle), ankle and trunk, where flexion, extension and lateral flexion are tested. Passivité, or degree of lack of reaction to passive stretching, is assessed by noting the amount of passive movement, flapping or 'ballant' imparted to a limb or part of it (hand, arm, foot, leg) on shaking it. The third aspect is the consistency of muscles or palpation. Tonus and the primary automatic responses or reflexes, of which automatic walking is the best known (and the source of much pleasure to parents and professional alike), are the twin pillars on which the neurological examination rests; the contribution of more conventional methods in this age-group is very limited.

In this book Claudine Amiel-Tison, a third generation disciple of André-Thomas, and Albert Grenier, describe their experience with neurological assessment during the first year of life. It is a short book, but an important one. The first chapter considers the various demands made of developmental neurology by the many interested parties, obstetrician, parents, neonatologist, physio-therapist, neuropsychiatrist and epidemiologist. The outcome of the very low birth weight infant is discussed and Swedish experience of the large number of lives saved without cerebral palsy is quoted in support of a positive balance sheet.

Two chapters deal with the neurological examination in the neonatal period and normal development in the first year, with clear descriptions and good photographs and line drawings to illustrate the various manoeuvres. Clinical gradation of the full term newborn is made at the end of the first week, partly because in France the postnatal hospital stay has been 6 to 7 days, and partly because this time corresponds to the disappearance of most minor neurological signs linked to the birth process.

The fourth chapter is, for me, the most remarkable and exciting. It describes the 'complementary neuromotor examination' (CNME) and raises many fascinating questions. This examination of the newborn and young infant has been used by the authors since 1970 to expand and enrich the findings of the classical neuromotor examination with the goal of identifying soon after birth infants who do *not* have CNS dysfunction and of predicting a normal outcome for both motor and cognitive function as early as possible. The authors describe the process of enlisting the active participation of the infant in the examination by bringing him from his usual state of involuntary and undirected activity to one in which he interacts with the examiner in a state of enhanced alertness and potential for a more mature pattern of motor activity. This state is additional to and far in advance of the conventional five 'states' of Prechtl used in grading the newborn infant's behaviour. The authors describe this process as 'debugging' (not the happiest phrase). This process depends on making and maintaining close contact and rapport with the infant and on temporarily suppressing the Moro reflex, which is responsible for the greatest amount of involuntary 'parasitical' movements in the infant up to 3 months of age, when reflex motor activity spontaneously disappears. This suppression is achieved by manually fixing the infant's neck so that he will react as if he already had the degree of head control which normally occurs only at 3 months of corrected age. His motor activity is then 'liberated' from the involuntary reflex motor activity which interferes with all spontaneous movements. In this liberated state it is possible to enter into a far closer visual, auditory and tactile contact with the infant than is normally possible, and to demonstrate, under ideal conditions, a 'liberated' motor performance far in advance of his actual age. In the 'Récamier position', lying on either side, with his head supported by the examiner, as if reclining on a divan, the infant of 6 or 8 weeks can be brought actively to raise himself upright into a sitting position, by pressure on his uppermost hip. The authors do not yet have statistics on long-term outcome regarding this reaction, but believe that it must indicate 'a sound central organisation, incompatible with cerebral damage', a belief which seems very reasonable. They describe also the reaction of lateral abduction of the hip, obtained in the young infant in the liberated state, which in their experience is always absent in children with a motor handicap, even before the handicap can be confirmed clinically. This corresponds to an equilibration reaction usually noted in older children at about the eighth month. This reaction, described and illustrated in detail, was found to correlate well with neurological outcome at age one year or more, since none of those in whom it was present showed later cerebral motor handicap, while this was found in half of those in whom the reaction was absent.

The value of a method which could allow early positive affirmation of normality is clear when one considers the frequency with which cerebral palsy is overdiagnosed, as shown by recent North American studies in which motor anomalies observed in half of over 200 children classified as handicapped in their first year turned out to be transient.

The significance of such transient neuromotor anomalies and their correlation with difficulties at school age is discussed in another chapter in relation to 'minimal brain damage', a term which, though not ideal, is probably no worse than those proposed to replace it. The authors argue, largely from earlier findings of Drillien in low birth weight infants, that some children with transient neuromotor dysfunction in the first year graduate to join the ranks of those who at school age show signs of cerebral deficit. The ability to predict which infants at risk might do so and which would not, if confirmed, prove of great value in planning and in counselling parents.

Speculation also comes permissibly to mind as to whether the techniques of the complementary neuromotor examination, by promoting and anticipating activities appropriate to an older age, may

possibly have a beneficial effect in speeding up the rate of development in a more permanent fashion. To assess the results of physiotherapy in young children is notoriously difficult, but an attempt to determine this question seems worthwhile.

The translation is excellent. My only quibbles are to strain at 'debugging' (and to wonder what was the French word it translates) and 'impotence of the neck'; if both seems risible to the English reader, it is a case of 'honi soit qui mal y pense'.

This is a delightful and stimulating book which should make many paediatricians itch to try their hands at the examination, and will give them expert guidance on how to do it. Paediatric physiotherapists, too, should find it of great interest. We should be grateful to André-Thomas for his pioneer work, and to his successors for developing it and for describing it so elegantly.

E. M. BRETT

**Deep Dyslexia.** Edited by M. Coltheart, K. Patterson and J. C. Marshall. 1986. Pp. 444. London: Routledge and Kegan Paul. Price £8.95.

**Surface Dyslexia. Neuropsychological and Cognitive Studies of Phonological Reading.** Edited by K. E. Patterson, J. C. Marshall and M. Coltheart. 1985. Pp. 544. Hillsdale, NJ: Lawrence Erlbaum. Price £29.95.

In 1973, Marshall and Newcombe published their seminal paper on acquired disorders of reading. They suggested that there existed two acquired disorders of reading: deep dyslexia and surface dyslexia, involving selective deficits within the domain of reading in contrast to pure alexia without agraphia. The years since the publication of that paper have seen a burgeoning of research on acquired disorders of reading, notably in England and now spread through the international neuropsychological community. What was a speculation of two disorders in 1973 is now generally accepted as fact. The two volumes under review bring together an impressive selection of reports on each of these disorders under the editorship of leaders in the field. *Deep Dyslexia*, edited by Coltheart, Patterson and Marshall, is a recent paperback edition of papers produced out of a 1978 symposium on the topic which were originally published in hardcover in 1980. The passage of years has made this volume no less timely and essential to anyone interested in the neuropsychology of reading than it was when originally published. *Surface Dyslexia*, edited by Patterson, Marshall and Coltheart, is an equally important contribution to the field. In both volumes the papers are thoroughly and well referenced, and each contains detailed indices, the more recent volume having commendable name and subject indices.

Most theorists of reading would argue that there are two routes available for reading aloud the word *dog*. By one route, there is direct access to the mental lexicon and the word's semantic and syntactic properties; the lexical information is then directed to a mechanism for phonological interpretation and ultimately realized in speech. It is just such a mechanism which is required for reading ideographic orthographies such as Chinese characters. By the second route, the word is broken down into sublexical units, for example, the graphemes *d-o-g*; these units are assigned a phonological interpretation which serves as the input to the lexicon, on the one hand, and the mechanisms for speech realization, on the other. A route such as this would seem to be required for reading nonsense words such as *turp*. While there is general acceptance of the dual route model, there is considerable debate within the field as to the specific details of each route. The General Introduction to *Surface Dyslexia* provides an excellent overview of the dual-route models, and the papers in both these volumes offer clear and thoughtful characterizations of the areas of agreement and debate.

Deep dyslexia is generally taken to involve a compromise to the ability to translate orthographic representations directly into phonological representations. As would be predicted by any dual-route models, deep dyslexics are unable to read nonsense words. Beyond that, a fascinating range of systematic reading errors in deep dyslexics provide important insights into the mechanisms of the direct orthographic recognition route. Deep dyslexics make semantic errors (e.g., reading *uncle* as *cousin*), derivational errors (e.g., reading *wise* as *wisdom*), visual errors (e.g., reading *stock* as *shock*),

and have a striking inability to read function words such as *and* and *the*. The opening two chapters of *Deep Dyslexia* by Marshall and Newcombe and by Coltheart provide an excellent concise overview of the phenomenology of the disorder. Surface dyslexia, by contrast, is hypothesized to involve an impairment to the route which allows lexical access from orthographic representations without an intermediate step of phonological analysis. In a language such as English, the analysis correctly predicts significant difficulty in reading phonologically irregular words (e.g., *rough*, *dough*, *through*) and overgeneralization of grapheme-phoneme correspondence rules (e.g., pronouncing the *t* in *listen*). Regrettably, *Surface Dyslexia* lacks the detailed introductory chapters of the earlier volume, though the editors do provide a serviceable overview in their introduction to the first section of the book. Case Studies of Acquired Surface Dyslexia.

Among the most fascinating chapters in each volume are those by Sasanuma on acquired reading disorders in Japanese. In Japanese there are two orthographies, the Kanji and the Kana. The Kana is a syllabary while the Kanji is ideographic. The base forms of nouns, verbs, and adjectives are typically given in Kanji; grammatical formatives, word endings and function words are only written in Kana. The dual-route models of deep and surface dyslexia predict that there should be patients in which reading in one but not the other orthography is impaired. In detailed reports on a range of patients, Sasanuma presents a wealth of data demonstrating the disassociability of reading aloud Kanji and Kana. In addition to a paper on Japanese in each volume, *Deep Dyslexia* contains a paper on the disorder in a speaker of French by Andrews, Deloche, and Kossanyi, and *Surface Dyslexia* contains two papers dealing with speakers of French, one by Kremin and the other by Goldbrum, as well as papers dealing with the reading of Spanish and Kannada, a Dravidian language by Masterson, Coltheart and Meara and by Karanth, respectively. The bulk of the papers in each volume deals with studies of reading English aloud by such notables in the field as Marshall, Newcombe, Shallice, Warrington, Coltheart, Patterson, Marcel, and Morton. Throughout both volumes, cases are clearly presented and considerable neuropsychological data are provided on the subjects; presentation of neurological data is less consistent.

Each volume concludes with a brief section on the anatomical loci of lesions in some of the patients presented. *Deep Dyslexia* contains a short report of CT scans from 5 patients by Marin plus a brief postmortem report by Shallice and Warrington. Marin notes that in all cases the lesions are extensive both cortically and subcortically; no specific communalities were found among the cases. Vanier and Caplan provide an analysis of CT and postmortem data from 7 surface dyslexics. Vanier and Caplan speculate that posterior damage, specifically involving superior temporal lobe structures, is necessary, though they report 1 case where the lesion was restricted to the right hemisphere.

There are no final answers in the behavioural or neurological analyses of deep and surface dyslexia. *Deep Dyslexia* and *Surface Dyslexia* are no less valuable for that. These volumes, which present carefully and thoughtfully researched studies by the leading neuropsychologists studying acquired reading disorders, will be of primary interest to neuropsychologists and students of the psychology of reading. The detailed accounts of symptomatology will provide an accessible compendium of information on reading and reading-related disorders to practising clinicians as well.

MARY-LOUISE KEAN

**Aspects of Epilepsy and Psychiatry.** Edited by Michael R. Trimble and Tom G. Bolwig. 1986. Pp. 256. Chichester: John Wiley. Price £24.50.

This is an effective book that brings together material on the psychiatry of epilepsy that is not readily available elsewhere. How does it compare with *Epilepsy and Psychiatry* (Churchill Livingstone) of which Dr Trimble was also coeditor. Although there are obvious considerable areas of overlap, particularly useful amongst the chapters in *Aspects of Epilepsy and Psychiatry* is one on aggression and epilepsy written by Peter Fenwick, and based upon the very considerable experience at the Institute of Psychiatry and the Maudsley Hospital in this field. Although Dr Fenwick specifically

excludes the episodic dyscontrol syndrome from discussion, I would have been interested to see in this context more information about the relationship between this syndrome and epilepsy. Even though carbamazepine is used in the treatment of both, episodes of dyscontrol probably do not have a basis in a seizure discharge, but we badly need some longitudinal epidemiological studies.

Mogens Dam and Agnete Mouritzen Dam review the old chestnut of 'Is there an epileptic personality?', underlining the point that many of the observed changes may well be due to the expectation of unpredictable and uncontrollable unpleasant events, rather than to changes in neural organization associated with the epilepsy itself.

Another interesting chapter is by Mary Robertson on the problem of depression in patients with epilepsy. Although she makes every effort, in her own study, to distinguish between misery and sadness at facing the problems associated with having epilepsy, and a true depressive illness, difficulties clearly remain. She reports that, in a double blind placebo controlled trial in 42 patients with depression and epilepsy, there was no difference in outcome at six weeks between the two antidepressant drugs and placebo. I am sure that she is right in advising that, when confronted by a miserable or depressed patient with epilepsy, it may be wise to withhold antidepressants for a time during which some exploration of ongoing problems can be undertaken.

There are a number of other good chapters, useful amongst which is one by Brian Toone exploring the causes of impaired sexuality among men with epilepsy, and an unusual chapter by Jolyon Oxley, J. W. A. S. Sander and P. J. Thompson reviewing epilepsy as a chronic handicap. The last paragraph of this chapter and of this book contains a message that all of us who deal with epilepsy should remember, based upon the survey of doctors' perspectives of epilepsy undertaken a few years ago by Beran and colleagues. Beran *et al.* concluded that '(There are) some real and disturbing areas of concern, since the therapists themselves are implicated as a source of the negative attitude directed against epileptic patients. . . . (There is) a real need to reappraise the approach to teaching the medical profession about epilepsy. There is a definite lack of knowledge, a lack of ability to maintain critical evaluation, and an apparent lack of awareness that these problems exist.'

### Reference

BERAN RG, JENNINGS VR, READ T (1981) Doctors' perspectives of epilepsy. *Epilepsia*, **22**, 397-406

ANTHONY HOPKINS

**Clinical Neurosurgery**, Volume 33. Congress of Neurological Surgeons. 1986. Pp. 702. London: Williams and Wilkins. Price £54.00.

Even measured by the high standards achieved in previous volumes in this series, Volume 33 of *Clinical Neurosurgery* based on the proceedings of the 1985 Congress of Neurological Surgeons in Honolulu, contains material of exceptional value and interest to the practising neurosurgeon. The 41 chapters cover an unusually wide range of topics, almost all of them relevant to general neurosurgical practice. Some of the chapters are paired, with different experts putting the case for and against a particular surgical procedure. This is done for microlumbar discectomy, chemonucleolysis, and surgery for unruptured cerebral arteriovenous malformations. Other topics covered include the in utero treatment of ventriculomegaly, antibiotic prophylaxis in neurosurgery, the treatment of brain abscess, emergency and posterior circulation revascularization procedures, surgery for cervical radiculopathy and spinal metastases, and the microvascular procedures for vertigo. Yet again we have chapters on the optimum timing of aneurysm surgery and the use of antifibrinolytic treatment. There are 4 chapters on different aspects of the management of low grade glial tumours. A careful reading of these chapters made this reviewer wonder if he should not adopt a less conservative approach to this common problem both as regards surgery and radiotherapy. Undoubtedly the most important

chapter in this book is the succinct account by Dr S.J. Peerless of the design, management and results of the multicentre randomized double blind controlled study of intracranial-extracranial bypass. The implications of this study are profound and far reaching for all branches of surgery, not just for neurosurgery. This is the first time that a major neurosurgical operation has been eradicated by such a trial. It will probably not be the last. Most of us know in our hearts that many of the operations we perform would not survive such an objective assessment.

Almost all of this volume of *Clinical Neurosurgery* is well written and stimulating. As always, it is well bound, well printed, well illustrated and fairly priced. Every neurosurgeon should buy it.

R. S. MAURICE-WILLIAMS

**Subarachnoid Haemorrhage. Aneurysms and Vascular Malformations of the Central Nervous System.**

By R. S. Maurice-Williams. 1987. Pp. 431. Bristol: Wright. Price £55.00.

For one man to gather together and refer to 1,231 publications in the field of subarachnoid haemorrhage is a considerable labour; and for this we have to be grateful to Robert Maurice-Williams. The bibliography includes 1985 references, which, in the light of the usual delays between submission of manuscripts and publication, is acceptable for a book published in 1987, particularly on a subject which is constantly evolving. The subject headings extend from the historical background, through aetiology, pathology, physiological consequences of haemorrhage, clinical diagnosis, epidemiology and natural history, and treatment of patients with intracranial aneurysms. In addition the book deals with intracranial arteriovenous malformations and spinal subarachnoid haemorrhage.

In reviewing a book which attempts to cover all aspects of a subject which forms a very major part of most active neurosurgeons' work, one seeks first the author's objectives. This is clearly stated in the Preface: 'This book is presented as a review of current knowledge about the conditions that may cause subarachnoid haemorrhage and their management. It is aimed at the general physician, the neurologist and the neurosurgeon in training'. Such an objective is laudable, but is it achieved?

The chapter on historical background provides an enjoyable and succinct preamble to the main bulk of the book, and in it the author is at his best in style and direction. But as the reader—and even one who has considerable personal knowledge and experience in the subject—proceeds through the book, there is a sense of being submerged by an extensive and at times uncritical literature review of complex and often controversial matter. Thus references to clinical work based upon 3 cases should hardly have a place in a book with the objectives as defined. Readers who seek references and guidance upon specific topics will have to turn to different sections of the book; thereby it is difficult to avoid repetition. This is exemplified by 'spasm' which is discussed in the sections on pathology, natural history, preoperative management, physiological consequences of haemorrhage, and the results of surgery.

Sadly it is for the general physician and the neurologist, the author's first chosen audience, that the book is least successful. Unless the physician and the neurologist are using the book as a ready reference manual to the bibliography, they will be disappointed (as was this reviewer) by the relative lack of clearer conclusions and guidelines. Nowhere is this more apparent than in the subjects of timing of surgery and management results, both of which are crucial to the physician and the neurologist, who are responsible for initiating correct management. To draw attention to results showing that overall management at 3 months after haemorrhage produces only 42% of patients without neurological deficit, is valuable provided that the author gives guidance in correlating this with the natural mortality and morbidity facing an individual patient for whom the physician or neurologist is responsible. Until a major defect in British neurological training is remedied and a period in a neurosurgical service becomes obligatory, the neurologist will continue to need the printed word; that will always be second best.

Why the author decided that it seemed inappropriate to intrude his own experience and opinions into a review of this kind is difficult to understand. Any neurosurgeon producing such a book would



be expected to have a very considerable personal experience of the subject, particularly in its clinical and surgical aspects. Had the author more clearly 'intruded' his own experience and opinions, it might well have enhanced the value of the book.

JOHN GARFIELD

**Advances and Technical Standards in Neurosurgery**, Volume 14. Editor-in-Chief, L. Symon. 1986. Pp. 230. Wien: Springer-Verlag. Price DM 148.00.

Since *Advances and Technical Standards in Neurosurgery* was established in 1974, there have been 14 volumes in this series which is intended as a pan-European contribution to neurosurgical postgraduate education. Each volume has been arranged in two parts: a first part on advances both in neurosurgical techniques and in related sciences, and a second part in which acknowledged experts discuss standard surgical procedures, giving others the benefit of their considerable experience. In this volume the advances section consists of chapters on intracranial endoscopy, the use of evoked potentials in neurosurgery and hypothalamic neuropeptides. The technical standards section is devoted to sphenoid ridge meningiomas and congenital cord tumours in children. For the first time a brief third section has been introduced — a sort of round table forum in which the members of the editorial board discuss their differences in the practical management of some common problem. The topic they have chosen is the intraoperative management of ruptured aneurysms.

The conception of this series was admirable, but this volume disappoints as have so many of its predecessors. As always it is a mixed affair, excellent in parts but much of it unreadable, either because of a turgid prose style or because of an excess of technical and scientific detail which is irrelevant to neurosurgical practice. The reasons for this failure probably arise from a lack of firm editorial control together with the multinational character of the series. The necessity for the contributors to come from a range of European countries means that many of the articles in this series have been written by authors whose grasp of the English language and its prose style are less satisfactory than they may realize.

The edible portions of this curate's egg of a book are contained in the chapters on endoscopy, evoked potentials, and congenital cord tumours in children. Sadly these good parts comprise only a relatively small proportion of the whole. *Advances in Technical Standards* is beautifully produced and illustrated but for the neurosurgeon who seeks to keep abreast of advances, it does not begin to compete with that other annual series *Clinical Neurosurgery*. Perhaps it is time for the Editorial Board to bring this series to a close.

R. S. MAURICE-WILLIAMS

**The Blood-brain Barrier in Health and Disease**. Edited by A. J. Suckling, M. G. Rumsby and M. W. B. Bradbury. 1986. Pp. 207. Weinheim: VCH Verlagsgesellschaft. Price DM 98.00.

The blood-brain barrier serves as an important regulatory mechanism for the chemical environment in the central nervous system and changes in its function are, as we all know, very important in many disease processes afflicting the brain and the spinal cord. It is therefore understandable that many symposia and other forms of scientific meetings are focused on the blood-brain barrier and that there already exist several review articles and monographs in this field of research.

The question is, then, does this book of 207 pages provide the reader with anything new which cannot be obtained in existing monographs and review articles, and does it have a place in the library of neuroscientists. My answer to these questions is in the affirmative for several reasons. The book is composed of 14 chapters written by experts covering different areas of research on the blood-brain barrier and many of the chapters, for instances Crone's chapter on the barrier under normal conditions, and Bradbury's chapter on the role of endothelial cells for barrier breakdown, are very

up-to-date, easy to understand and very useful as a source of recent knowledge in this field of research.

The first part of the book is concentrated on the function of the barrier under normal conditions and the second on pathological changes in the barrier. The editors have selected a few important areas in which the barrier plays an important role in pathological conditions. They include chapters on barrier dysfunction and its consequences in inflammatory conditions and intoxications. It should be emphasized that the book does not give a complete coverage of all aspects of barrier dysfunction, which probably was not the goal of the editors.

I would like to recommend this book to everyone interested in the blood-brain barrier in health and disease and it can serve as a very good complement to the more extensive monographs already in this area.

YNGVE OLSSON

**The Bramwells of Edinburgh: A Medical Dynasty.** By Bryan Ashworth. 1986. Pp. 96. The Royal College of Physicians of Edinburgh. Price £12.00.

Dynasty—a word only six years younger than printing with movable type itself—is currently undergoing semantic trial by television, but the descendants of George Bramwell of Elswick in Lancashire confidently adopted the motto 'Like begets like', joined the Eugenic Society and were evidently planning a long reign; however, on the evidence presented the case proposed by the Honorary Librarian of the Royal College of Physicians of Edinburgh is not perhaps proven.

Byrom Bramwell was taught by figures influential in the development of 19th Century neurology including Thomas Laycock and David Drummond of Newcastle, and himself taught a younger generation that included S. A. Kinnier Wilson, Risien Russell, James Taylor, W. J. Adie, J. G. Greenfield and R. Marcus Gunn. There were failures in his career—he earned only 5 guineas in his first year in Edinburgh practice and never secured the coveted chair of Medicine—and successes—he was the first FRCP (London) not first to have been awarded membership of the College, fellowship coming at the age of 77 in the same year as his knighthood. Byrom Bramwell's publications are distinguished; he wrote monographs on Diseases of the Spinal Cord (1882) and Intracranial Tumours (1888) in which he made original observations on hypothalamic-pituitary connections. He also wrote on cardiovascular medicine and haematology (analysing 14,777 cases of anaemia) but the breadth of his medical scholarship is represented by 8 volumes of the quarterly journal *Clinical Studies* which he wrote himself between 1903 and 1910, and the 2 volumes of *Studies of Clinical Medicine* (1889–1890) containing verbatim accounts of his Friday clinical demonstrations from May 3, 1889 to March 21, 1890, presumably modelled on Charcot's *Leçons du Mardi*; these contain many informative diagrams but Bramwell's ability to illustrate his writings is best demonstrated in the 3 folio volumes of his *Atlas of Clinical Medicine* published between 1892 and 1896. These 13 volumes of clinical material receive only brief mention by Dr Ashworth, and perhaps the paterfamilias of his putative dynasty also deserves a more informative epitaph than 'He was a very nice man.'

Byrom begat Byrom, who studied at the Bar and two medical sons, Edwin and John Creighton Bramwell (J. C. B.). Bryan Ashworth is understandably less enthusiastic about the sons than their father; we do not learn much of Edwin's neurological training in Germany, or with Dejerine and the other 'famous people' he encountered, so that after a difficult start in Edinburgh during which father encouraged him to leave, it is a surprise suddenly to find Edwin sitting comfortably, but part-time, in the chair of medicine. His writings were not numerous and there were no monographs, but he gave the inaugural paper to the Association of British Neurologists (on aneurysm and third cranial nerve palsy). The biographical section on J. C. B. outlines his career as cardiologist and physiologist in Manchester under a variety of personal and professional headings; the short obituary notice of Byrom junior is reprinted from the *Genealogist's Magazine*.

There are chapters dealing with the Royal College and some Medical Societies in Edinburgh, and

on postgraduate teaching and examinations. These provide further details of Edwin Bramwell's administrative abilities and justify the laudatory remarks made by Russell Brain in his annual address as president of the Royal College of Physicians of London in 1952. In his paper to the Edinburgh Harveian Society, Edwin Bramwell is credited with the apocryphal remark that 'Sir Charles Bell did for the nervous system what Harvey did for the circulation'; Bell himself first hinted at this generous analogy which was obligingly endorsed by his brother-in-law Alexander Shaw. Dr Ashworth describes how the medical Bramwells attempted to operate the principle of taking from the rich and giving to the poor in levying their fees, but they were often exploited by unscrupulous patients claiming impecuniosity or financial immunity on other grounds. We learn of their recreational interests and the main text ends quietly on a fishing trip in Norway.

One third of the book consists of appendices which include Byrom Bramwell's memories of the heroes who crowded his medical schooldays, and there is an especially interesting account of James Syme who was twice appointed to the chair of surgery in Edinburgh. Edwin Bramwell's paper on contributions by Edinburgh alumni to the neurology of pupillary responses, including his own introduction of the eponym 'Holmes Adie syndrome' for myotonic pupils, is reprinted and updated to 1985 by Bryan Ashworth. Lastly, Byrom senior's remarks on making a will in the context of aphasia are reproduced, in which he reiterates the advice that questions expecting the answer 'yes' should be varied with those requiring a 'no' sufficiently to demonstrate that the patient's intentions have been unambiguously established.

There are many household names in the history of 19th Century neurology and Byrom Bramwell deserves to be amongst them. This pleasantly produced book will undoubtedly stimulate interest in Bramwell and his sons; Dr Ashworth's readers, with whetted appetites, will now want to know more.

ALASTAIR COMPSTON

**Electrodiagnosis in Clinical Neurology.** Second edition. Edited by Michael J Aminoff. 1986. Pp. 755. Edinburgh: Churchill Livingstone. Price £65.00.

The second edition of this book continues the policy of introducing the reader to the scope of clinical electrophysiology by describing those procedures which have achieved clinical relevance. Progress over the six years since the successful first edition is reflected in the increase in chapters from 17 to 22. Ten of the original contributions have required only small modifications and two have undergone more substantial up-dating, including Chatrian's reappraisal of the electrophysiological evaluation of brain death, which now includes a good bibliography of the vigorous debate on this topic a few years ago. New authors have altered the emphasis of some chapters in line with current practice; there is an excellent review of somatosensory evoked potentials by Eisen and the editor. The article on neuromuscular transmission has more on single fibre EMG and a useful table on the congenital myasthenias. There are completely new chapters on ambulatory EEG monitoring (Ebersole), brainstem auditory evoked potentials in paediatrics (Picton and coworkers) and evoked potential techniques for intraoperative monitoring (Grundy), all of which have developed considerably in recent years, and there is much more information than previously on certain aspects of EMG including late responses (Shahani), the blink reflex (Kimura) and evaluation of tremor and central disorders of movement (Hallett). There is a good new chapter on event-related potentials by Goodin, though its inclusion probably reflects the editor's interest rather than general acceptance that this aspect of evoked potentials is of proven clinical value.

This volume succeeds admirably in its aim of providing a general guide to the role of electrodiagnosis in neurology: the layout is good and the contributions are in general clear and concise.

N. M. F. MURRAY

**Neurotransmitter Interactions in the Basal Ganglia.** Edited by M. Sandler, C. Feuerstein and B. Scatton. 1987. Pp. 271. New York: Raven Press. Price \$52.00.

The clear involvement of basal ganglia in the production of movement disorders has made them a focal point for neuroscience research. As a consequence, the neuronal connections within the basal ganglia are well characterized, their transmitter substances largely identified and the physiology and pharmacology of the area extensively documented. Yet despite the considerable attention that the basal ganglia have received, their true function remains a mystery and the advent of sophisticated new techniques has revealed a level of organizational complexity previously unknown.

The present volume contains a series of camera-ready manuscripts dealing with newer aspects of basal ganglia organization. These presumably represent the proceedings of some unspecified meeting which, from the references quoted, took place in the latter part of 1985. In general I have a low opinion of conference proceedings as a means of producing an authoritative text. However, this volume is a pleasant surprise and certainly ranks among the better books resulting from a heterogeneous meeting. Indeed, the editors are to be congratulated on the organization of the volume and the quality of its content.

Of particular interest are the series of chapters dealing with the patchwork or striosomal organization of striatum. This clearly throws new light on the functional organization of this brain region. I found the chapter by Dr Gerfen on the neostriatal mosaic to be stimulating and to provide the best summary of transmitter organization within the striatal patches and matrix currently available. Similarly, Fuxe and colleagues present an excellent, although diverse, overview of the mosaic organization of the striatum which is spoilt only by the tiny print accompanying the figures and tables.

Others sections of the book cover acetylcholine, GABA, glutamate and peptide involvement in basal ganglia organization from a variety of viewpoints. The chapters by Glowinski's group provide an insight into the complexity of control of dopamine and GABA release. Gonon and colleagues and Di Chiara and coworkers illustrate the use of *in vivo* voltammetry and *in vivo* dialysis as new techniques for studying basal ganglia transmitter interactions. Similarly, Drs Palacios and Wiederhold illustrate how the use of the 2-<sup>14</sup>C-deoxyglucose techniques can be employed to study neurotransmitter interaction in brain and to fingerprint the pharmacological profile of novel pharmacological agents.

Overall, this is a volume I very much enjoyed reading and certainly one I will refer to over the ensuing years. I would recommend the book to all interested in basal ganglia function as a text which clearly sets out the current approach to many areas of basal ganglia research.

P. JENNER

## ANNOUNCEMENTS

### International Symposium on Generalized Epilepsy

An International Symposium on cellular, molecular and pharmacological approaches to generalized epilepsy will be held in Montreal, Quebec, Canada, on June 11–13, 1988. Further details may be obtained from Ms T. Maglietta, Coordinator, Room 710, Montreal Neurological Institute, 3801 University Street, Montreal, Quebec, Canada H3A 2B4. Telephone (514) 284-5852.

### European Neurological Society

The European Neurological Society (ENS) has been founded to foster cooperation between neurologists and those working in related disciplines within Europe. Meetings will be held biennially. The participation of individuals from other areas of the world is welcomed. The biennial meetings will provide instructional courses for neurologists in training, up-date symposia, and sessions for the presentation of original work, either as platform or poster presentations. The first meeting will be held in Nice from June 19–21, 1988, when the teaching programme will include courses on peripheral neuropathy, neuroimaging, ageing and dementia, and neurovirology/neuroimmunology. There will be symposia on physiological and pathological aspects of cerebral blood flow, clinical neuropharmacology, and neurogenetics.

Active membership of the ENS will be by election from clinicians and scientists whose chief interest is directed towards practice, teaching or research in neurology and cognate fields. Active membership will become effective only after contribution to a meeting of the ENS. Junior members may be elected from members engaged in postgraduate studies in neurology or related disciplines.

Further information about the ENS, together with registration and abstract forms for the first meeting, may be obtained from the Secretary, Professor G. Said, Service de Neurologie, Hôpital de Bicêtre, 94287 Le Kremlin Bicêtre Cedex, France. Abstract forms must be returned by February 1, 1988.

#### **Queen Square Alumni Meeting in New York**

An organizational meeting for an Alumni Association for the National Hospital, Queen Square, was held on April 8, 1987, during the annual meeting of the American Academy of Neurology. Present at this meeting were neurologists from the United States, Canada, United Kingdom, and the Federal Republic of Germany. There was a definite feeling that an Alumni Association should be formed. During the next twelve months, further details of organizing the Association will be investigated. All physicians who have studied or been affiliated with the National Hospital at Queen Square are welcome to participate. Future meetings for interested Alumni will be held at the 1987 American Neurological Association meetings and at the 1988 American Academy of Neurology annual meeting. Individuals interested in learning more about the organization are asked to write to Dr John C. Steiner, 1095 Nimitzview Drive, Cincinnati, Ohio 45230. Individuals interested in meeting at the American Neurological Association meeting should write to Dr Michael F. Finkel, 733 W. Clairemont Avenue, PO Box 1510, Eau Claire, WI 54602-1510.

#### **Ninth International Symposium on Parkinson's Disease**

The Ninth International Symposium on Parkinson's Disease, under the auspices of the Research Committee on Extraparallel Diseases of the World Federation of Neurology will be held in Jerusalem, Israel, on June 5-9, 1988. Further information may be obtained from the Secretariat, PO Box 50006, Tel-Aviv 61500, Israel. Telephone (03) 654571. Telex 341171 KENS IL.

#### **National Academy of Neuropsychologists (USA)**

The National Academy of Neuropsychologists will hold its Seventh Annual Meeting on October 28-30, 1987, at the Palmer House Hotel in Chicago, Illinois. It will include several full day and half day workshops, special topic symposia, keynote address, and poster sessions. For further information and registration materials, contact Dr Antonio Puente, Department of Psychology, University of North Carolina, Wilmington, NC 28403, USA. Telephone (919) 395-3812.

#### **New York Academy of Sciences: Conference on the Structure and Function of Calcium Channels**

A conference will be held at the Royal Society, London, UK, on July 18-20, 1988. This will provide a forum for a multidisciplinary discussion based on recent developments in electrophysiological and biochemical studies of  $Ca^{++}$  channels. The major aim will be to contribute towards a better scientific understanding of the relationship between the structure and function of  $Ca^{++}$  channels.

There will be a contributed poster session. The deadline for the submission of abstracts is January 31, 1988. These should not exceed 200 words and should be sent to Dr Dennis Wray, Academic Department of Pharmacology, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF, England. For programme and registration information, contact the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021. Tel (212) 838-0230.

#### **Ninth International Meeting on Neuromuscular Diseases**

This will be held in Marseille on September 15-17, 1988. Further information may be obtained from Professor G. Serratrice, 9th Journées Internationales de Pathologie Neuromusculaire, CHU La Timone, 13385 Marseille Cedex 5, France.

#### **Second Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference**

This conference will be held at Camelback Inn Resort, Scottsdale, Arizona on March 6-9, 1988. For information, contact Toby Jardine, Special Projects Coordinator, Barrow Neurological Institute, 350 West Thomas Road, Phoenix AZ 85013. Telephone (602) 285-3178, or 1-800-BARROW-1.

**Fifteenth Annual Symposium, Barrow Neurological Institute**

This symposium, which will be devoted to selected topics on ischaemic and haemorrhagic cerebrovascular disease, will be held at Camelback Inn Resort, Scottsdale, Arizona, on March 10-12 1988. For information, contact Toby Jardine, Special Projects Coordinator, Barrow Neurological Institute, 350 West Thomas Road, Phoenix AZ 85013. Telephone (602) 285-3178, or 1-800-BARROW-1.

## *Travel Grants For Young Neuroscientists*

The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
  - (a) an abbreviated curriculum vitae and a list of any relevant publications;
  - (b) statement of age and post currently held;
  - (c) a concise account of the purpose of the proposed visit;
  - (d) a recommendation from the head of department (where appropriate);
  - (e) a letter of acceptance from the department to be visited;
  - (f) a statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always be taken of reduced air fares when available.
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# Brain

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2. Optometrists with a PhD degree who wish to extend their research experience.
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4. Clinicians with a training in pathology or ophthalmology who wish to pursue an academic career in ophthalmic pathology.
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These Fellowships may be held in appropriate departments or clinical centres in the United Kingdom of Great Britain and Northern Ireland. In cases where the necessary research training cannot all be obtained in the U.K. the Trustees are prepared to consider a request that part of a Fellowship be spent in a suitable centre or centres abroad. The Trustees are particularly aware of the desirability for clinicians in vision research of obtaining a basic science training, if necessary in a department away from the recognised centres of ophthalmological excellence. There is considerable flexibility in the kind of Fellowship support that might be offered, and candidates are welcome to discuss their plans with the scientific staff of the vision research section of the Trust.

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## SERVICE TO NEUROSCIENCE

# A CASE OF INTEGRATIVE VISUAL AGNOSIA

by M. JANE RIDDOCH and GLYN W. HUMPHREYS

*(From the Department of Paramedical Sciences, North East London Polytechnic, and the Cognitive Neuropsychology Research Group, Department of Psychology, Birkbeck College, University of London)*

## SUMMARY

A single case study of a patient with visual agnosia is presented. The patient had a marked impairment in visual object recognition along with good tactile object identification and a preserved ability to copy. Detailed investigations demonstrated impaired perceptual processes, with the patient's identification strongly affected by duration of stimulus exposure and by using overlapping figures. However, his stored knowledge of objects was shown to be intact. The results demonstrate that agnosia may be determined by a specific deficit in integrating form information; and that the input description for visual object recognition, disrupted in this patient, is functionally separate from stored object descriptions, which are intact. The implications of the results for understanding visual agnosia and for theories of normal visual object recognition are discussed.

## INTRODUCTION

Visual agnosia is a severe modality-specific deficit in the recognition of visually presented objects. It is a recognition, rather than a naming deficit, since visual agnostic patients are unable to gesture the use or to show any recognition of the objects they fail to name. Typically, discussions of visual agnosia centre around Lissauer's (1890) distinction between apperceptive and associative agnosia. Lissauer argued that visual object recognition was composed of two primary independent stages; apperception, the process of constructing a perceptual representation from vision; and association, the process of mapping a perceptual representation onto stored knowledge of the object's functions and associations. Lissauer proposed that, following brain damage, patients may be impaired in either the apperception or the association process, with both impairments giving rise to a deficit in visual object recognition.

There have been several cases documented where visual object recognition deficits appear to be consequent on an impairment in establishing adequate perceptual representations of visual forms. For instance, the patient reported by Efron (1968) and Benson and Greenberg (1969) appeared to be impaired at almost any task requiring the discrimination of shape, despite having intact discrimination of size.

intensity, distance and movement (*see also* Campion and Latto, 1985; Campion, 1987). Clearly such an impairment in using even simple shape information will render object recognition deficient. According to Lissauer's definition, such patients appear impaired in the apperception process.

In contrast to the above types of patient, other patients with visual object recognition deficits may be relatively good at copying the objects they fail to recognize (e.g., Rubens and Benson, 1971; Ratcliff and Newcombe, 1982) and at matching photographs of objects taken from different viewpoints (e.g., Taylor and Warrington, 1971; Warrington, 1975). Indeed, Riddoch and Humphreys (1987) have recently documented the case of a patient who was poor at matching objects on the basis of their associative relations, and yet who was good at discriminating pictures of real objects from pictures of meaningless distractors which were closely matched for visual similarity relative to their real counterparts (an 'object decision task'; *see* Experiment 3 below). With such closely matched distractors, object decisions may only be made with reference to stored knowledge about an object's structure. Thus the latter case suggests that impaired visual access to functional and associative knowledge about objects may occur in the presence of intact access to stored structural knowledge. Clearly this case indicates that visual object recognition may be impaired in the presence of a normal perceptual representation of the visual world, consistent with a deficit in what Lissauer termed the association process.

The distinction between apperceptive and associative agnosia introduced by Lissauer emphasizes a two-stage view of visual object recognition. More recent accounts of the recognition process, while consistent with a two-stage view, also propose that both the apperception and the association stages may themselves be divided into various substages (e.g., Marr, 1982; Humphreys and Riddoch, 1987). The latter accounts predict that it is possible for each of these substages to be selectively impaired following brain damage and, therefore, for different types of 'apperceptive' or 'associative' impairment to result. Indeed, it may be that patients previously classed as either apperceptive or associative agnosics may illustrate damage only to some substages.

In the present paper we report a detailed case study of a patient, H.J.A., with a marked and selective deficit in visual object recognition. This recognition deficit seems to be of a higher order than that sustained by the apperceptive agnosic patients studied by Efron (1968), Benson and Greenberg (1969), Campion and Latto (1985) and Campion (1987). Yet we present evidence for its being consequent on a residual impairment in perceptual representation. We therefore suggest that the classification scheme for agnosia be expanded to incorporate such selective deficits in particular substages in visual perception.

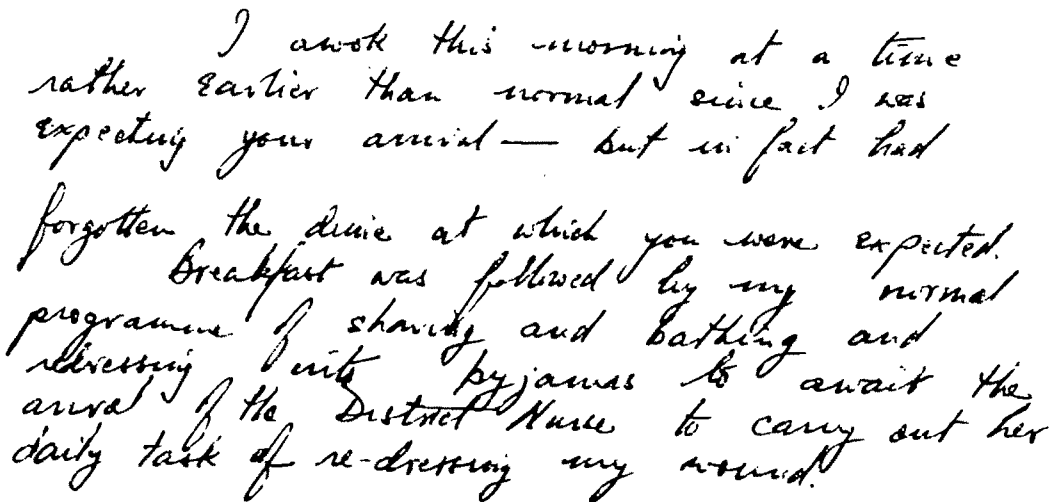
The paper is organized as follows. In Section 1, we discuss H.J.A.'s performance on a series of diagnostic tests used to classify patients in terms of the apperceptive-associative agnosic dichotomy. The subsequent sections are then devoted to investigations of other aspects of H.J.A.'s recognition performance. Section 2 deals with



H.J.A.'s recognition performance. Section 3 deals with his semantic knowledge and access to such knowledge from vision. Section 4 deals with his short and long-term visual memory. Section 5 deals with his ability to use context to facilitate object recognition. H.J.A.'s visual recognition impairment is attributed to a primary deficit in his perceptual representation of visual stimuli, and this deficit coexists along with intact semantic and visual memory, and an intact ability to make use of context. The implications of the case for accounts both of visual agnosia and the processes mediating normal object recognition are discussed.

### CASE HISTORY

Details of H.J.A.'s case history have been given elsewhere (Humphreys and Riddoch, 1984). Premorbidly, he was an executive who held responsibility for the European transactions of an American company. He suffered a stroke perioperatively in April, 1981, when aged 61 yrs. Subsequent to the stroke, his major problem was an inability to recognize common objects and faces by sight. He had acquired achromatopsia, showing a complete inability to discriminate colours. He also showed topographical agnosia, in that he was unable to recognize his environment by sight and he could easily become lost if moved away from a well-learned route. His reading was reduced to an accurate but slow letter-by-letter process. He had only a minor writing problem (see fig. 1), but was



I awoke this morning at a time  
rather earlier than normal since I was  
expecting your arrival — but in fact had  
forgotten the date at which you were expected.  
Breakfast was followed by my normal  
programme of shaving and bathing and  
dressing in pyjamas to await the  
arrival of the District Nurse to carry out her  
daily task of re-dressing my wound.

FIG. 1. Example of H.J.A.'s handwriting.

typically unable to read what he had written (the reading of handwriting being a particularly difficult task for letter-by-letter readers; see Warrington and Shallice, 1980). H.J.A. had no memory deficits (digit span 8–9; see Sections 3 and 4 in the text for discussion of his semantic memory, his memory of the structural characteristics of objects, and his short-term visual memory).

An initial CT scan (May 1981) failed to reveal any marked neurological abnormalities, but a subsequent scan (June 1984) demonstrated extensive infarction extending forward in both occipital lobes in the distribution of the posterior cerebral arteries (see fig. 2). Perimetric testing (using both the Goldman and the Octopus apparatus) showed a superior altitudinal defect of both the left and right visual fields (see fig. 3). Responses from the lower fields were normal. Snellen acuity was normal.



FIG. 2. CT scan, June 1984, showing bilateral occipital infarction.

Visual evoked potential recordings showed normal patterns to stimuli presented to his lower visual fields, and no response to stimuli in his upper fields. Eye movements were recorded by both infrared and search coil techniques. Smooth pursuit movements (infrared recordings) were normal, as were horizontal saccades and downward vertical saccades to random targets at steps of 30 deg (search coil recordings). Vertical saccades upwards showed a staircase tracking pattern, consistent with his superior altitudinal field defect (*see* fig. 4). No motor deficits were apparent, or expressive or receptive speech problems.

The present investigations were carried out in a number of sessions conducted between April 1981 and May 1985 during which time H.J.A.'s condition remained stable. The only slight improvement observed was in the visual recognition of very familiar household objects (knife, fork, spoon, cup, etc.). He was well orientated in time and place during all the test sessions.

## NEUROPSYCHOLOGICAL INVESTIGATION

### *Section 1. Diagnostic tests*

H.J.A. named 28/45 real common objects correctly from vision, but 36/42 of the same objects from tactile presentation. Tactile identification was reliably better than visual identification ( $\chi^2 = 5.02, P < 0.05$ ). However, real objects were easier to identify from visual presentation than photographs of the same objects taken from a prototypical viewing position (21/32 vs 12/32; McNemar test of change,  $\chi^2 = 4.90, P < 0.05$ ). This shows that H.J.A.'s problem in identifying objects is modality specific, and sensitive to the visual information present in the stimulus. His identification is better given the extra information present in real objects.

When H.J.A. failed to identify objects correctly, he was unable to gesture their use. On simple function match tasks, involving the matching of line drawings or photographs of physically-different objects which can be used for the same function (*see* Warrington and Taylor, 1978), he performed poorly, scoring 12/20 with line drawings and 18/26 with photographs. His performance on the function-match

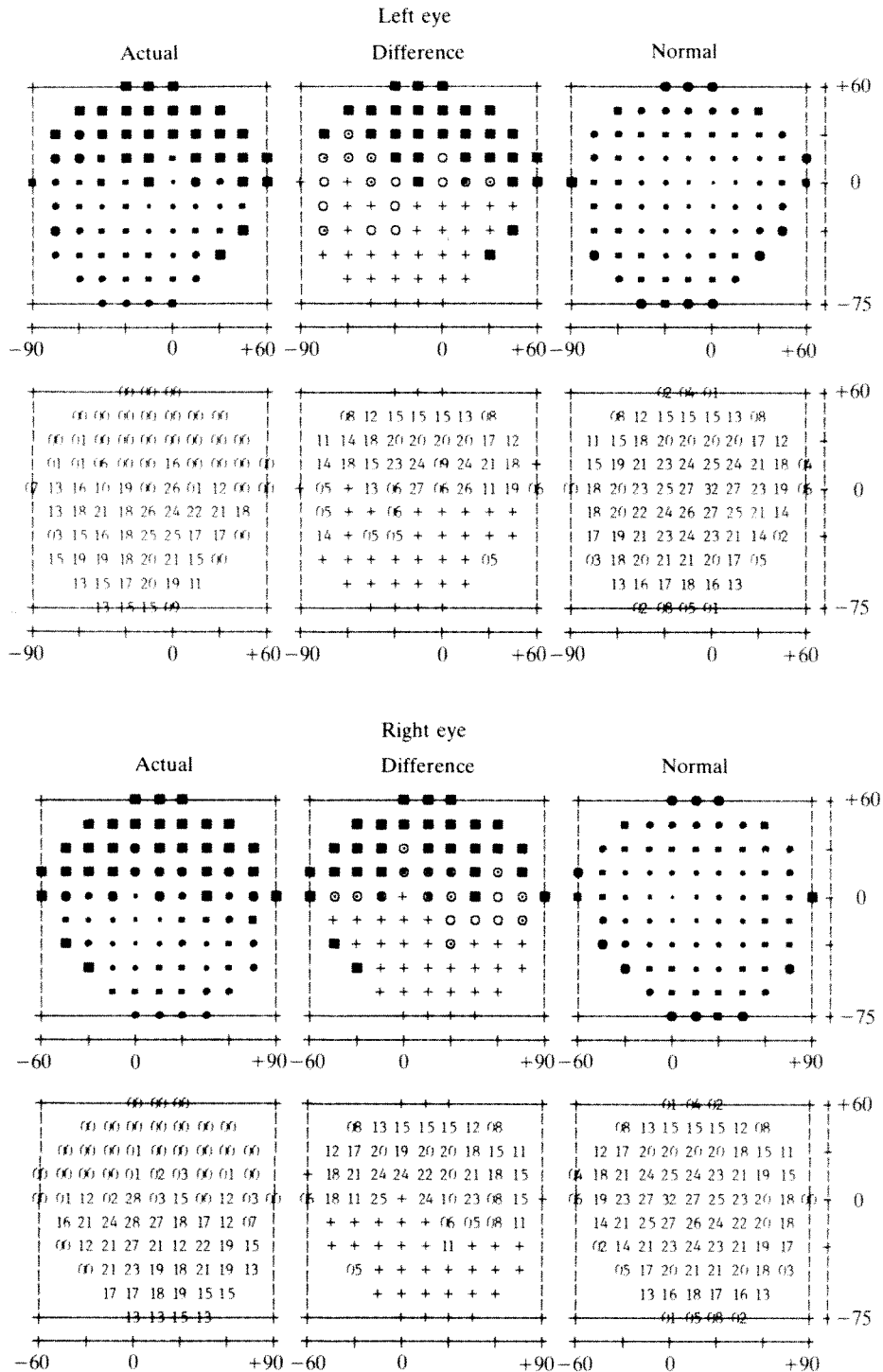


FIG. 3. Results of Octopus perimetric recordings of H.J.A.'s visual fields.

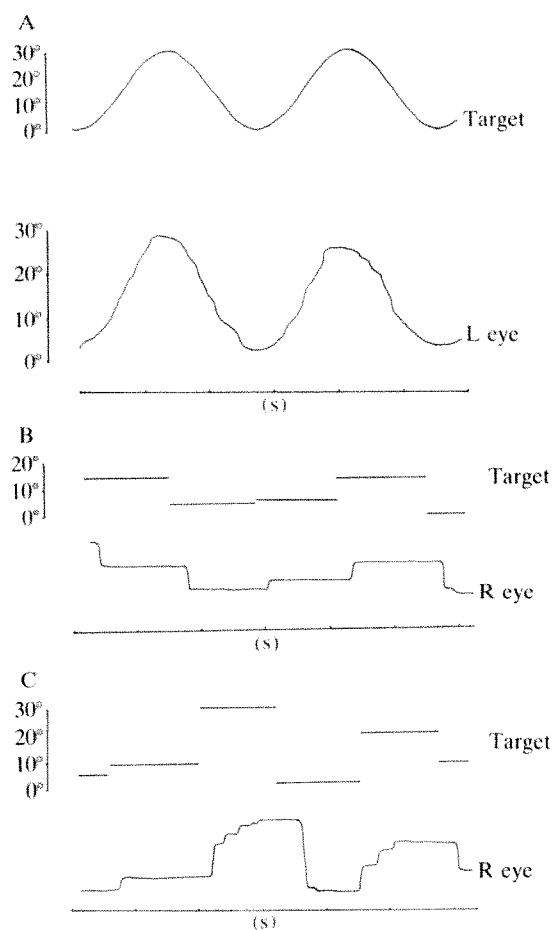


FIG. 4. Examples of H.J.A.'s eye movement recordings. A, smooth pursuit movements; B, horizontal saccades; C, vertical saccades. Smooth pursuit movements of both the left and the right eyes were made. Only left eye movement is shown here.

task with photographs was worse than his ability to perform 'physical' match tasks. For instance, it was worse than his matching of photographs of foreshortened objects across different viewpoints (24/26; *see* Humphreys and Riddoch, 1984; Fisher Exact Probability  $P=0.03$ ). The function-match task is not more difficult than different-view matching task, as right hemisphere-damaged patients who are impaired at different-view matching can find the function-match test easier (e.g. D.B., reported in Humphreys and Riddoch, 1984, scored 23/36 on the function match test and 12/26 on the foreshortened-view test  $\chi^2=8.74$ ,  $P<0.01$ ). H.J.A. is relatively impaired at matching objects on the basis of their functions. Also, his function match performance was related to his ability to name the objects used ( $Z=1.71$ ,  $P<0.05$ ; Kendall's Tau = 0.374 for the line drawings;  $Z=2.05$ ,  $P<0.025$ , Kendall's Tau = 0.398 for the photographs). There was no reliable relation between his different-view matching performance and his ability to name the objects involved

( $Z < 1.0$ ; Kendall's Tau = 0.091). Thus he can match objects across different viewpoints without knowing their identities, whilst he tends not to know the function of objects when he fails to identify them. This confirms that the problem is not simply one of naming.

H.J.A. typically named stimuli using deliberate articulated feature-by-feature descriptions, irrespective of whether the stimuli were real objects, line drawings or photographs. An example of a feature-by-feature description is given in Fig. 5. There were also indications of incorrect grouping of the local parts of objects. For instance, when shown a photograph of a paint-brush with a wooden handle, H.J.A. responded that 'it appears to be two things close together; a longish wooden stick and a darker, shorter object, though this can't be right otherwise you'd have told me'.

In nearly all cases H.J.A.'s naming latencies were abnormally prolonged, being of the order of 25 s for correct responses and 41 s for incorrect responses. Such long latencies suggest that his visual object recognition is typically based on an extensive search of his stored knowledge about objects. Errors occur when he fails to match the input with his stored knowledge and, on such occasions, he seems to carry out an exhaustive search of his stored knowledge until a partial match occurs.

H.J.A. made solely visual naming errors or omissions. This suggests a problem in gaining access to semantic and name information from vision, perhaps because he has difficulty attaining an appropriate perceptual representation. At any rate, his failure to make any semantic errors is contrary to the proposal that his recognition deficit reflects an impaired semantic system (*see* Riddoch and Humphreys, 1987).

H.J.A. also tended to find objects from categories with 'structurally similar' exemplars (e.g., animals, birds, fruit, insects and vegetables) more difficult to identify than objects from categories where the exemplars tend to have more distinctive structures (e.g., body parts, clothing, furniture, implements and vehicles) (*see* Riddoch and Humphreys, 1987). He named 24/40 line drawings of objects from categories with structurally distinct exemplars and 12/35 objects from categories with structurally similar exemplars. This difference is statistically significant  $\chi^2 = 4.87$ ,  $P < 0.05$  (*see* Appendix for arguments concerning other accounts of this result).

The consistency of H.J.A.'s performance was assessed by re-presenting 25 of the line drawings from both the structurally similar and the structurally distinct categories. He named 16/25 (session 1) and 17/25 (session 2) of the objects from the structurally distinct categories, and 9/25 (session 1) and 8/25 (session 2) of the objects from the structurally similar categories. For both category types, his performance was close to that expected if there was perfect consistency across the sessions, whilst performance differed from that expected if there were complete independence.

For the structurally distinct objects, H.J.A.'s overall probability of correct naming was 0.66. Assuming complete independence, he would score 10.89

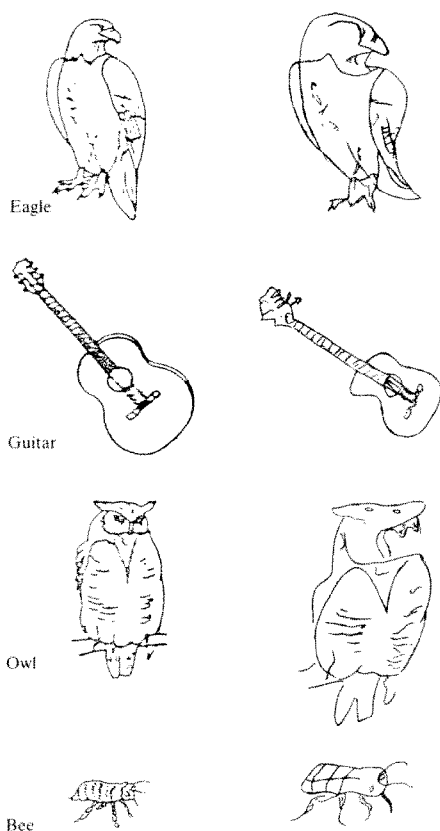


FIG. 5. Examples of H.J.A.'s copying of objects he fails to identify. In each example, the original line drawing is shown on the left and H.J.A.'s copy is shown alongside it. He named the eagle as 'a cat sitting up', the guitar as 'some kind of a machine, a press', the owl as 'a pattern', and the bee as 'an animal with horns and a tail, a rhino'.

( $0.66 \times 0.66 \times 25$ ) correct on both occasions, the number of stimuli which he names correctly on one occasion and incorrectly on the other should be 5.61 ( $0.66 \times 0.34 \times 25$ ), and the number which he fails to name on both occasions should be 2.39 ( $0.34 \times 25$ ). The observed frequencies (15 correct on both occasions, 2 correct on the first and incorrect on the second, 1 correct on the second and incorrect on the first, and 7 incorrect both times) differ significantly from those expected from complete independence ( $P < 0.05$ , goodness of fit with 3 deg of freedom). The observed frequencies are also close to those expected from complete dependence (16.5, 0, 0, 8.5). Finally, if there was complete independence, performance accuracy in the second test should be the same for the items wrong on the first test as for the items right. Out of 9 errors on test 1, only 2 were correct on test 2; out of 16 correct responses on test 1, 15 were correct on test 2. Performance on the items wrong on test 1 differed from that on the items correct ( $\chi^2 = 10.46$ ).

Equivalent results obtained in the analysis of his performance on structurally similar objects.

In contrast to his poor visual object recognition, H.J.A. was good at copying objects. Examples of some of his copies of line drawings, which he failed to identify, are given in fig. 5.

### *Summary of the diagnostic tests*

H.J.A. is impaired at recognizing visually presented objects. This impairment is most severe for line drawings and least severe for real objects. Nevertheless, even with real objects he is worse when they are presented visually than when they are presented tactilely. H.J.A.'s visual recognition performance is consistent across items, and is characterized by slow feature-by-feature descriptions. His naming errors are always visually related to the target objects, suggesting some form of deficit in perceptual representation. However, H.J.A. is able to copy objects which he shows no sign of recognizing, and he can match objects accurately across at least some transformations of viewpoint. Thus he has a marked deficit in visual object recognition along with at least some intact elementary perceptual functions. For instance, intact copying indicates the ability to trace contours visually and to mark the positions where breaks in inspection occur (*see* Ullman, 1984). H.J.A.'s intact copying, alongside his visual recognition impairment, might be taken to suggest a classification in terms of associative agnosia. In the following sections, we examine various aspects of H.J.A.'s object recognition system in more detail so that we may better understand the exact nature of the deficit. Of particular interest was whether H.J.A.'s perceptual representation from vision was impaired, despite his good copying and different-view matching.

## *Section 2. Tests of perceptual representation*

### *General examination*

Previous work suggested that H.J.A. had relatively good perception of the component dimensions of visual form; he showed normal discrimination of line length, orientation and position (Humphreys and Riddoch, 1984). He also performed quite normally on a series of standard illusions (the Necker cube, the Müller-Lyer, Ponzo and Zöllner illusions), indicating sensitivity to depth information induced by local form cues. H.J.A. was further able to perceive subjective contours. For instance, he described Kanizsa's triangle (Kanizsa, 1976; Frisby 1979, p. 118) as 'two triangles superimposed: the points of one triangle pass over and to the centres of three surrounding solid circles'. He could also see depth from stereo disparity information when shown filtered anaglyphs of random dot stereograms (Julesz, 1971).

We also examined H.J.A.'s ability to detect ambiguities in pictures. He was able to detect some ambiguities in the Hogarth engraving given in Gregory (1970, p. 51); for instance, the 'rod held by the eighteenth century gentleman is ridiculous since

it reaches too far, right over to the horse and cart'. This suggests that he is able to see more than one object at a time, that he can perceive depth by perspective and that he can interrelate objects coded at different depths. The descriptions also suggest that he is better able to identify objects in context than out of context; for instance, he is typically unable to identify a horse shown in isolation and yet he had no especial difficulty in identifying horses paired with a cart (though this was done very slowly; see Experiments 15 and 16 below for a more detailed investigation of the effects of context on identification).

### *Experiment 1. Overlapping figures*

So far we have documented that H.J.A. has preserved acuity, analysis of contour, use of local depth information and use of local feature cues, in addition to our earlier report of intact discrimination of line length, orientation and position (Humphreys and Riddoch, 1984). However, there are examples where H.J.A.'s perceptual representation seems impaired, such as his naming errors due to incorrect segmentation of objects into their parts.

To examine H.J.A.'s ability to segment visual information more formally, a test requiring the identification of overlapping figures was devised. The test comprised three sections, respectively, requiring the identification of letters, geometrical shapes, and line drawings of common objects. In each section the stimuli were either presented singly, in nonoverlapping groups or in overlapping groups. There were 5 such conditions for the letter and geometrical shape sections: single stimuli, nonoverlapping pairs, overlapping pairs, nonoverlapping triplets and overlapping triplets. The line drawing section contained only the single stimuli, the non-overlapping pairs and the overlapping pairs.

The stimuli were presented on single sheets (21.5 cm  $\times$  32 cm). Single letters were about 1 cm in height  $\times$  0.8 cm width and they were spaced 7 cm apart on the sheet (6 rows with 3 targets per row). Single geometric shapes were about 1.4 cm in height  $\times$  1.4 cm in width, and they were spaced similarly to letters. The line drawings of single objects were about 3.5 cm high  $\times$  4 cm wide, and they are spaced 12 cm apart (6 rows with 2 targets per row). In the paired and triplet conditions there were gaps of at least one character size between the groups. The line drawings were all drawn from a set of stimuli which H.J.A. had been able to identify on previous occasions. All the sheets were viewed from a height of about 40 cm.

H.J.A.'s performance was compared with that of 8 age-matched control subjects (mean age 69.75 yrs, range 60–86 yrs). Subjects were presented with sheets from one condition at a time and they were asked to name the stimuli as quickly as possible, working from left to right across the page. The time taken to complete each sheet was recorded using a digital stopwatch.

If H.J.A. has no perceptual impairment but only a problem associating perceptual information with stored knowledge, he should not be differentially impaired in the overlapping figures condition (relative to the nonoverlapping, baseline conditions).



TABLE 1. MEAN CORRECT REACTION TIME (IN S) PER SHEET AND PER ITEM IN THE OVERLAPPING FIGURES TEST

| Conditions              | Controls  |          |           |          |              |             |
|-------------------------|-----------|----------|-----------|----------|--------------|-------------|
|                         | H.J.A.    |          | Mean      |          | Range        |             |
|                         | Per sheet | Per item | Per sheet | Per item | Per sheet    | Per item    |
| Letters                 |           |          |           |          |              |             |
| Single stimuli          | 11.50     | 0.639    | 7.93      | 0.441    | 5.83– 11.19  | 0.324–0.621 |
| Paired nonoverlapping   | 21.90     | 0.608    | 13.81     | 0.384    | 11.01– 22.56 | 0.251–0.627 |
| Paired overlapping      | 52.80     | 1.467    | 16.03     | 0.445    | 10.82– 25.66 | 0.300–0.713 |
| Triplets nonoverlapping | 33.60     | 0.622    | 22.29     | 0.413    | 14.34– 34.93 | 0.311–0.647 |
| Triplets overlapping    | 56.80     | 1.052    | 23.92     | 0.443    | 16.98– 35.14 | 0.314–0.651 |
| Geometrical shapes      |           |          |           |          |              |             |
| Single stimuli          | 26.80     | 1.489    | 18.35     | 1.019    | 12.37– 24.42 | 0.687–1.357 |
| Paired nonoverlapping   | 47.71     | 1.325    | 38.92     | 1.081    | 23.98– 65.18 | 0.666–1.811 |
| Paired overlapping      | 59.79     | 1.661    | 39.07     | 1.085    | 25.03– 65.91 | 0.799–1.831 |
| Triplets nonoverlapping | 80.70     | 1.494    | 65.03     | 1.204    | 35.09–133.93 | 0.650–2.480 |
| Triplets overlapping    | 137.79    | 2.552    | 69.19     | 1.281    | 32.83–136.94 | 0.608–2.610 |
| Line drawings           |           |          |           |          |              |             |
| Single stimuli          | 59.00     | 4.508    | 14.04     | 1.170    | 7.58– 40.9   | 0.631–3.410 |
| Paired nonoverlapping   | 72.99     | 3.042    | 21.48     | 0.895    | 11.49– 49.9  | 0.498–2.079 |
| Paired overlapping      | 118.59    | 4.942    | 23.87     | 0.995    | 12.79– 66.88 | 0.533–2.787 |

The mean correct reaction times (RTs) (s) per sheet and per item for H.J.A. and the control subjects are given in Table 1. No errors were recorded.

There was a consistent pattern of results across the three types of stimuli: relative to the control subjects, H.J.A. was differentially impaired in identifying overlapping relative to nonoverlapping stimuli. This is most clearly exemplified by his performance with letters, where the increase in RTs to individual stimuli when the stimuli were overlapping was ten times larger than the largest increases present in the control subjects. Similar effects were present with the geometrical shapes and the line drawings. In the overlapping figures test, all subjects saw the nonoverlapping forms first. For the control subjects, this led in some cases to faster RTs for the overlapping figures (e.g., with the line drawings). In contrast, H.J.A. was always slower with overlapping figures. His problem with overlapping figures occurs despite having just seen and identified the same stimuli.

H.J.A. is impaired at segmenting overlapping figures, relative to control subjects. This impairment is not stimulus specific. Since the conditions differed only in the amount of (presemantic) segmentation processes required, H.J.A.'s differential difficulty with overlapping figures is consistent with a deficit in presemantic perceptual processing.

Patients with other types of perceptual disorder also find the identification of overlapping figures difficult. For instance, we have recently screened over 50 patients for perceptual problems following cerebral vascular accidents. Of these

patients, 2 showed differential problems with overlapping figures of about the same magnitude as the effects observed with H.J.A. Both patients had suffered unilateral right hemisphere damage. One had ancillary deficits in simple perceptual matching tasks requiring judgement of line length and orientation; the other manifested unilateral neglect. In contrast, H.J.A. shows good line length and orientation discrimination (Humphreys and Riddoch, 1984), and full awareness of the spatial extent of stimuli (unlike the neglect patient). Unlike these other patients, it appears that H.J.A.'s problems in segmenting overlapping figures is isolated from problems in discriminating and using contour information, and it therefore represents a selective deficit.

### *Experiment 2. Object decision*

As a further test of H.J.A.'s presemantic perceptual processing, he was asked to perform a series of 'object decision' tasks. In all these tasks, the subject is presented with a series of line drawings. Half of the linedrawings depict common objects, half depict meaningless objects created by substituting or adding parts of different objects together. The subject is asked to decide which line drawings depict real objects and which depict meaningless objects.

As noted in the Introduction, Riddoch and Humphreys (1987) have reported data on a patient who performed object decisions normally but who was poor at matching visually presented objects related by functional association (e.g. hammer and nail). The latter result indicates that stored knowledge about the structure of objects can be separated from semantic knowledge about their function and prior association. Thus, the object decision task assesses the ability to access stored, pre-semantic structural knowledge. If H.J.A. has intact access to stored structural knowledge about objects, he should be able to perform object decisions normally; he may have difficulty only if he is unable to assemble an intact perceptual representation or if he has lost structural knowledge about objects.

*Experimental 2a. Object decision with line drawings.* Meaningless (distractor) objects were constructed in either one of two ways, half by substituting a feature from one real object (feature-replaced condition), the other by adding an incongruous feature to a real object (feature-added condition). The feature-replaced distractors should maintain the global shape of their parent objects better than

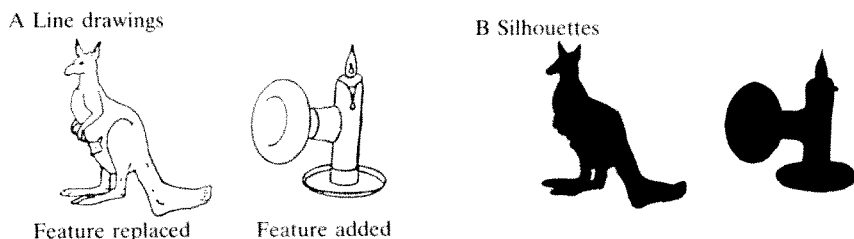


FIG. 6. Examples of the distractors used in the object decision task. A, feature-replaced and feature-added distractors used in Experiment 6a. B, silhouette distractors used in Experiment 6b.

the feature-added distractors. Categorization based solely on such global shape information should be worse on feature-replaced than on feature-added stimuli.

One hundred and twenty line drawings were used (from Snodgrass and Vanderwart, 1980). Of these, 60 were unadulterated (targets), 30 had a feature-replaced and 30 had a feature added (*see* fig. 6A). The stimuli were glued to cards and placed in a random order in front of the subject, who was asked to sort them into two piles, one for real objects and one for meaningless objects.

H.J.A.'s performance was compared with that of 11 control subjects (age range 40–60 yrs; mean age 52.5 yrs) without any history of neurological disorder. H.J.A. scored 69/120 correct (54.50%); the mean of the control subjects was 115.7/120 (96.44%), and the range was from 112/120 (93.33%) to 118/120 (98.33%). He was clearly worse than the control subjects at this task, and his performance on line drawings of real stimuli was at chance (29/60). His rejection of meaningless stimuli was slightly better if they were feature-added rather than feature-replaced (22/30 vs 18/30), though this difference was not statistically significant ( $\chi^2 < 1.0$ ).

H.J.A.'s poor performance on the object decision task indicates that he does not have intact access to stored structural knowledge of objects from vision; this may either be because his perceptual representation of the stimulus is impaired or because he has lost stored structural knowledge about objects.

In a follow-on experiment, we tested H.J.A.'s performance using the silhouettes of some of the stimuli from the first object decision task. If he has lost structural knowledge about objects, he should be equally impaired with silhouettes and line drawings.

*Experiment 2b. Object decision with silhouettes.* Silhouettes of 88 of the stimuli from the first object decision task were used (stimuli were omitted if they could only be identified from internal details); 44 depicted real objects (targets) and there were 22 feature-added and 22 feature-replaced distractors (*see* fig. 6B). The procedure was exactly the same as that used for the first object decision task. There were 11 new control subjects drawn from an age range between 45 and 74 yrs; the mean age was 66.44 yrs.

H.J.A. made 63/88 (71.59%) correct discriminations, which was reliably better than his performance on the first object decision task ( $\chi^2 = 4.04$ ,  $P < 0.05$ ). The mean of the control subjects was 77.73/88 (88.33%) and there was a range between 65/88 (73.86%) and 85/88 (96.59%). The performance of the control subjects on the object decision task with silhouettes was worse than that of the control subjects on the same task with line drawings ( $t(20) = 2.09$ ,  $P < 0.05$ , two-tailed).

H.J.A. is better able to perform object decisions on silhouettes of objects than on complete line drawings. This is not because silhouettes are inherently easier, since control subjects find them more difficult than complete line drawings. Presumably the contrast between his performance and that of the controls is a function of the reduced internal detail in silhouettes. Normally, internal detail adds more information about object identity and it facilitates the segmentation of an object into its parts. For H.J.A., however, internal detail hinders performance. Why

should this be so? His good copying indicates that he can discriminate the local parts of objects. Also, he appears to have some information about the global shape of stimuli, since he performs tolerably well with the silhouettes (*see also* Humphreys *et al.*, 1985). His problem seems to reflect an impairment in integrating local part information with information about global shape, in that local parts are treated separately and not grouped together to elaborate the global shape description. Thus he identifies objects from feature-by-feature descriptions, and adding the local detail in line drawings exacerbates the problem since it increases the amount of grouping that must take place.

### *Experiment 3. Tachistoscopic identification*

If H.J.A.'s visual identification is dependent on time-consuming feature-by-feature descriptions, we may expect it to be affected strongly by the exposure duration of the stimulus. Accordingly, we investigated his identification of line drawings and letters under tachistoscopic conditions.

*Line drawings.* Twenty line drawings of common objects (from Snodgrass and Vanderwart, 1980) were used, with the objects being chosen on the basis of H.J.A. correctly identifying them at least once on previous testing sessions. These line drawings were each presented at 4 durations: 100 ms, 500 ms, 1000 ms and unlimited (display terminated by the naming response). The stimuli and durations were presented in a fully randomized order, using a Cambridge Electronics two-field tachistoscope. Line drawings subtended a visual angle of about 2 deg in height by 2 deg in width. The first field contained a fixation cross which fell above each line drawing. H.J.A. was asked to name each depicted object. He named 16/20 of the objects with an unlimited exposure, 9/20 with a 1000 ms exposure, 8/20 with a 500 ms exposure and 3/20 with a 100 ms exposure. All his naming errors were visually related to the target, at each exposure duration. Normal subjects have no difficulty in identifying line drawings presented for 100 ms.

*Letters.* H.J.A. was first presented with a series of single letters at varying durations and then with a series of 2 letter stimuli. The letters were A, B, E, G and N, which could be presented in both upper and lower case. He was asked to name the letter(s) on each trial and, if possible, to report its case. Responses were counted as correct if he was able to report the letter name.

For single letter targets, there were 6 durations: 1000, 500, 100, 50, 25 and 10 ms. For 2 letter targets, only the first 5 durations were used. The stimuli were presented using a three-field Electronics Development tachistoscope. The luminance of both the fixation and the presentation field was 10 cd/m<sup>2</sup>, measured by a spot photometer. Single letters subtended a visual angle of 0.7 deg visual angle; two-letter targets were presented in a horizontal row and subtended a visual angle of about 1.8 deg. Letters fell beneath the fixation cross.

H.J.A. was told the set of target letters and that 1 or 2 letters would be presented, and he was asked to guess if unsure. The durations were varied randomly within

TABLE 2. NUMBER OF CORRECT IDENTIFICATIONS BY H.J.A. TO SINGLE AND TWO-LETTER TARGETS AS A FUNCTION OF THE EXPOSURE DURATION

|                                   | <i>Duration of exposure (ms)</i> |            |            |           |           |           |
|-----------------------------------|----------------------------------|------------|------------|-----------|-----------|-----------|
|                                   | <i>1000</i>                      | <i>500</i> | <i>100</i> | <i>50</i> | <i>25</i> | <i>10</i> |
| Single letters<br>(chance = 4/20) | 18/20                            | 18/20      | 18/20      | 18/20     | 6/20      | 0/20      |
| Two letters<br>(chance = 1.2/30)  | 23/30                            | 27/30      | 16/30      | 14/30     | 2/30      |           |

There were 5 target letter names which could be reported; therefore chance for single letters was 1/5, and chance for two letters was  $1/5 \times 1/5 = 1/25$ .

each single and two letter block. For the single letters, there were 20 exposures at each duration; for the two-letter targets, there were 30 exposures per duration. The number of correct identifications made at each exposure duration are given in Table 2.

H.J.A. was again affected by the exposure duration of the stimulus. For single letters, performance remained stable for exposures longer than 50 ms, while it fell to about chance at 25 ms. For two-letter targets, the accuracy of reporting both

TABLE 3. ERROR ANALYSES FOR SINGLE AND TWO-LETTER TARGETS.

Single-letter targets

| <i>Stimulus</i> | <i>Response</i> |          |          |          |          |
|-----------------|-----------------|----------|----------|----------|----------|
|                 | <i>A</i>        | <i>B</i> | <i>E</i> | <i>G</i> | <i>N</i> |
| A               | —               | 0        | 1        | 1        | 1        |
| a               | —               | 0        | 3        | 5        | 1        |
| B               | 1               | —        | 0        | 1        | 0        |
| b               | 1               | —        | 1        | 1        | 0        |
| E               | 1               | 2        | —        | 1        | 0        |
| e               | 1               | 0        | —        | 2        | 1        |
| G               | 0               | 2        | 1        | —        | 0        |
| g               | 5               | 1        | 2        | —        | 1        |
| N               | 3               | 0        | 0        | 0        | —        |
| n               | 2               | 0        | 1        | 0        | —        |

Two-letter targets

| <i>Stimulus</i> | <i>Response</i> |          |          |          |          |
|-----------------|-----------------|----------|----------|----------|----------|
|                 | <i>A</i>        | <i>B</i> | <i>E</i> | <i>G</i> | <i>N</i> |
| A               | —               | 0        | 0        | 1        | 2        |
| a               | —               | 1        | 4        | 10       | 2        |
| B               | 0               | —        | 0        | 2        | 0        |
| b               | 0               | —        | 3        | 1        | 1        |
| E               | 0               | 1        | —        | 1        | 2        |
| e               | 4               | 0        | —        | 2        | 0        |
| G               | 0               | 1        | 1        | —        | 1        |
| g               | 6               | 0        | 3        | —        | 2        |
| N               | 2               | 1        | 0        | 0        | —        |
| n               | 2               | 0        | 2        | 0        | —        |

letters decreased for exposure durations of 100 ms or less, although it also only fell to chance at 25 ms.

The identification errors made by H.J.A. for both single and two letter targets are shown in Table 3. He made similar patterns of errors for both. Lower case letters tended to be more difficult to identify than upper case letters, and systematic visual confusions tended to occur, particularly between lower case 'a' and 'g'.

H.J.A.'s errors to two-letter targets were further broken down as a function of the exposure duration and the error type (*see* Table 4). As the exposure duration

TABLE 4. TYPE OF ERROR RESPONSE MADE BY H.J.A. TO TWO-LETTER TARGETS AS A FUNCTION OF THE EXPOSURE DURATION

|   |                        | <i>Duration of exposure (ms)</i> |     |     |    |    |
|---|------------------------|----------------------------------|-----|-----|----|----|
|   |                        | 1000                             | 500 | 100 | 50 | 25 |
| a | 1 letter correct       | 7                                | 2   | 9   | 3  | 9  |
| b | Both letters incorrect | —                                | 1   | 1   | 3  | 9  |
| c | Omission (no response) | —                                | —   | —   | —  | 10 |
| d | 3 letters reported     | —                                | —   | 4   | 10 | —  |

decreased, he did not make more errors simply by reporting only one letter correctly; rather, proportionately more errors were made because he reported both letters incorrectly and because he started to make three-letter and omission responses.

H.J.A.'s visual identification of both letters and line drawings is markedly affected by the stimulus exposure duration. His performance at short durations is relatively better with letters than with line drawings, presumably because the letters have overlearned and simple patterns; nevertheless, his impairment is not limited to one stimulus type. For both letters and line drawings he tends to make visual errors. When two letters were presented there were stronger effects of exposure duration than when single letters were presented; however, the increased effects of exposure duration seemed to occur principally because he made more confusions between letters at the shorter durations, since he then began either to identify both letters incorrectly, to report three letters as present or to make omissions. These data suggest that, at the shorter exposure durations, there is increased interaction between the target stimuli with consequent impairments on identification performance.

### *Summary*

Our analysis indicates that H.J.A. has impaired visual perceptual processes, despite having some intact perceptual functions (local form discrimination, stereopsis and so forth). He is impaired at the identification of overlapping figures, relative to when the same figures are nonoverlapping; he is poor at discriminating line drawings of real and meaningless stimuli; and his visual identification is strongly affected by the exposure duration of the stimulus. His performance on the object decision task is improved when the stimuli are presented as silhouettes. H.J.A.'s

performance with silhouettes suggests that he has global form information available (*see also* Humphreys *et al.*, 1985). His difficulties seem to occur because his global form descriptions are not fully supported by more local form information, so that the segmentation of overlapping figures and the integration of local part information is impaired.

### *Section 3. Tests of semantic representation*

Given the controversy in studies of visual agnosia concerning whether agnosia is due to a perceptual deficit or to difficulties in mapping an intact perceptual information onto semantic descriptions, it is important to examine whether a patient has intact semantic knowledge of the stimuli he or she fails to recognize, since a recognition deficit could be precipitated by a breakdown in semantic knowledge about an object (*see* Warrington, 1975; Warrington and Shallice, 1984).

#### *Experiment 4. Verbal definitions*

H.J.A. was asked to give verbal definitions to a series of object names, all corresponding to pictures from the Snodgrass and Vanderwart (1980) picture norms. Thirty-two of the names fell between 0–20 occurrences per million in the Kučera and Francis' (1967) word frequency count and 22 fell between 21 and 274 occurrences per million.

He was able to give detailed definitions of all the objects, irrespective of their name frequency, and his definitions included details of the object's appearance. For example, his definition of a duck was as follows.

'This has two meanings. First, the noun version. A duck is a water bird with the ability to swim, fly and walk. It can be wild or kept domestically for eggs; when wild it can be the target of shooting. In the wild it has a wingspan between 15 and 18 inches and weighs about 2 or 3 pounds. Domestic ducks are heavier, up to about 6 pounds perhaps. Wild ducks are multicoloured, mainly brown but with green and yellow breasts. Domestic ducks are white or khaki.

There is also a verb version. Duck is a semislang word implying to lower the body to avoid being struck by a projectile or to avoid striking an obstruction with one's head.'

H.J.A.'s good ability to give verbal definitions suggests that he has intact semantic knowledge about objects. The precise nature of the semantic information he is able to access from vision and from auditory input was examined using a cued definitions test.

#### *Experiment 5. Cued definitions*

The task was an extension of the procedure developed by Warrington (1975). H.J.A. was asked a series of increasingly specific questions, following the visual presentation of an object or its name. These questions assessed whether he had sufficient knowledge to distinguish between objects within the same category (*see also* Riddoch and Humphreys, 1987).

The stimuli were 40 line drawings (from Snodgrass and Vanderwart, 1980) or their names, from 5 categories: animals, birds, insects, fruit and vegetables. For

each stimulus, a series of up to 11 probe questions were designed to assess both general and specific knowledge about an object (i.e., knowledge about an object's superordinate category vs item-specific knowledge). The specific questions tested stored functional, associational and visual knowledge. For example, for a 'horse', the questions included: can it be kept as a pet? does it eat meat? what colour is it? The objects had no verbal colour associations (see Beauvois, 1982; Beauvois and Saillant, 1985). The probe questions were the same for the auditory and visual presentations of the targets, with the exception that H.J.A. was asked the name of the object as a final probe question in the visual presentation condition.

The visual and auditory presentations were given in an ABBA design, with repetitions of stimuli spaced across different test sessions. The probe questions were spoken by the experimenter following the presentation of each target.

For the auditory presentation condition, H.J.A. made 120/120 (100%) correct responses to general knowledge questions and 219/225 (97.3%) correct responses to specific knowledge questions. There was no reliable difference between his performance with general and specific questions ( $\chi^2 = 1.84$ ,  $P > 0.05$ ). For the visual presentation condition, he made 100/120 (83.3%) correct responses to general knowledge questions and 148/225 (65.8%) responses to specific knowledge questions. His performance on both general and specific questions was better with auditory than with visual presentations ( $\chi^2 = 17.67$  and  $72.39$ , respectively, both  $P < 0.001$ ). Also, for visual presentations, he performed better on general than on specific questions ( $\chi^2 = 11.93$ ,  $P < 0.01$ ).

H.J.A. has good semantic knowledge of objects when accessed auditorily, but he is impaired at accessing semantic knowledge about the same objects from vision. The deficit in accessing semantic knowledge visually is manifest even with general questions, but it is most evident when the questions probe for semantic information specific to the given object.

It is interesting that H.J.A. was better able to answer questions testing general rather than specific semantic knowledge about the visually presented objects. This could be interpreted as reflecting a general degradation of his visual semantic knowledge about the tested objects, which may selectively impair specific knowledge prior to general category knowledge (see Warrington, 1975; Shallice, 1987).

Alternatively, good performance on general questions could reflect an ability to take advantage of visual cues in the stimuli, since such cues should be more relevant to general than to specific questions (Riddoch *et al.*, 1987). If the latter argument holds, then H.J.A. may be relatively good at other probe questions which may be answered using visual cues from the target. Interestingly, H.J.A. was surprisingly good at questions concerning the real-life size or weight of size-normalized drawings of the objects (when asked to judge the real size or weight of objects from Snodgrass and Vanderwart, 1980, relative to a reference object). For instance he made 30/40 (75%) correct weight classifications and named 21/40 (52.5%) of the objects correctly. The mean number of correct weight classifications for age-matching controls was 31.7/40 (79.2%), with a range between 29/40 (72.5%) and 36/40



(90%); their mean range of correct identifications was 35.3/40 (88.25%), range 33–40 (82.5–100%). A similar pattern of performance was found with size classifications, with H.J.A. within the normal range on size classification, while being markedly impaired at object identification.

Warrington (1975) used questions about the real size of objects to assess whether her patients had access to specific semantic knowledge about objects. However, since H.J.A. is otherwise impaired at accessing such knowledge, it appears that his good performance on size and weight judgements reflect the judicious use of visual cues. Indeed, he reported that he was able to classify the weight and size of many animals by judging the size and muscularity of the legs relative to the length of the body. It is important to note that quite accurate judgements may be made on this basis irrespective of whether the subject is able to access specific semantic information about the object. Unfortunately, the same is also likely to be true of other questions in cued definitions tasks addressed to pictorial stimuli (particularly so for the general questions): for this reason, cued definitions tasks might best be regarded as providing information about the kinds of knowledge patients have difficulty accessing (i.e., when patients fail), rather than as providing information about the semantic information to which they have access (i.e., when they succeed).

### *Summary*

H.J.A. has good conceptual information about objects which he cannot recognize visually when he is given their names. He also shows good ability to make use of pictorial cues to answer probe questions, even when there are no signs of correct semantic access for the given object (such as correct identification or an appropriate gesture). It seems quite possible that, in tasks such as cued definitions, H.J.A. is able to use visual cues to compensate for a profound deficit in the normal recognition process.

### *Section 4. Visual memory*

Although H.J.A. is able to give detailed verbal definitions of objects which he fails to identify visually, this may only be considered an assessment of his verbal semantic knowledge of objects; he may still have impaired semantic knowledge about the visual characteristics of objects. Such an impairment may or may not co-occur with a deficit in visual memory. To assess these possibilities, we investigated his ability to draw objects from memory, his memory for colours and his ability to maintain new visual information.

In at least some patients classified as associative agnosic, a disturbance in drawing objects from memory has been observed even when the patient is relatively good at copying (e.g., Levine, 1978; Ratcliff and Newcombe, 1982; but see Rubens and Benson, 1971; Wapner *et al.*, 1978). Agnosic patients have also been reported as having poor visual memory (Newcombe and Ratcliff, 1975; Wapner *et al.*, 1978; J.P. Davidoff, J. Wasserstein and B. Wilson, unpublished observations). It is

possible that these disturbances, either alone or in combination, could underlie the recognition deficit.

#### *Experiment 6. Drawing from memory*

H.J.A. was able to draw from memory objects which he typically failed to recognize from vision. This suggests that he has intact stored knowledge about the appearance of objects. Examples of these drawings are given in fig. 7.



FIG. 7. Examples of H.J.A.'s drawing from memory. H.J.A.'s drawing is on the left; alongside each of his drawings is a drawing from memory carried out by a control subject.

#### *Experiment 7. Stored knowledge about colours*

Recently, Beauvois (1982) and Beauvois and Saillant (1985) have presented data indicating that our stored knowledge of verbal colour associations is separate from our stored (visual) knowledge of the colour of objects having no verbal colour associations since, following brain damage, patients may be impaired at retrieving the different forms of colour knowledge from different input modalities. Thus tests of stored colour knowledge need to differentiate between knowledge which is associated verbally with an object and knowledge which reflects the visual properties of the stimulus.

Unfortunately, tests of H.J.A.'s visual colour-related knowledge using at least

some of the procedures developed by Beauvois are hampered by his acquired achromatopsia. He now cannot detect letters in the Ishihara charts, and he is impaired at matching colours to sample (where he confuses between dark colours and between light colours, presumably because his matching is based on brightness). This means that it is difficult to use visual tests of colour knowledge. We therefore assessed his colour knowledge by a series of auditory questions concerning the colour of objects with no obvious verbal colour associations (e.g., what is the colour of a frog, a radish, a polar bear, a banana, etc.) or verbal colour associations (e.g., what is the colour associated with a jealous person, a lime, snow, a communist, coal, etc.). He was asked one question at a time and he responded verbally with a colour name. He made 27/30 (90.0%) correct responses to the verbal colour associations and 20/28 (71.33%) correct responses for objects without obvious verbal colour associations. The difference between the tests failed to reach significance ( $\chi^2 = 2.15$ ,  $P > 0.05$ ). H.J.A.'s 3 errors to the verbal colour associations were on questions which required him to assimilate an abstract concept (what is the colour associated with an embarrassed/depressed/afraid person). However, for objects without obvious verbal colour associations, he made some errors which would be surprising were his visual colour knowledge intact (e.g., the colour of an elephant was named as green, that a polar bear, grey). These errors, plus the trend for worse performance on objects without obvious verbal colour associations, suggest that there may be some impairment in accessing stored visual knowledge of colour. Such a result would follow if the mechanisms used for colour perception are also those involved in visual colour memory (see Allport, 1985).

#### *Experiment 8. Maintaining visual information*

H.J.A.'s ability to maintain new visual information was examined using a letter-match technique (Posner, 1969). He was presented with a pair of letters and asked to respond 'same' if the letters had the same name and otherwise to respond 'different'. On half the trials when the letters had the same name they were also physically identical (e.g., AA), and on the other half the letters with the same name were physically dissimilar (e.g., Aa). Normally, RTs to identical letters (AA) are faster than responses to name-match letters (Aa), providing the interstimulus interval (ISI) is no greater than about 2 s (and the to-be-matched letters are not superimposed; see Walker, 1978). The difference between physical (AA) and name (Aa) matches may be attributed to subjects using a visual code to match identical stimuli; however, this visual code decays over time so that the physical-match advantage is typically lost with an ISI of over 2 s.

The apparatus and stimuli were the same as those used in Experiment 3. There were 5 possible letters, A, B, E, G and N, which could be in either upper or lower case. These letters were chosen to minimize the visual similarity between their upper and lower case versions. The to-be-matched letters were either presented simultaneously or with 1 or 2 ISIs: 700 and 1500 ms. H.J.A. initially focused on a central cross, and following a verbal prompt, the first letter was presented (for

500 ms) just below fixation. There was then an ISI, during which the fixation field returned, followed by the second letter, which remained present until he responded. Vocal responses ('same' or 'different'), measured by a voice key which stopped a Birkbeck timer. There were 40 trials at each ISI; 10 physical-match, 10 name-match and 20 different trials. On the different trials, random letters were paired together.

TABLE 5. REACTION TIME (RT, IN MS) AND PERCENTAGE ERROR FOR H.J.A. IN A LETTER-MATCH TEST AT DIFFERENT INTERSTIMULUS INTERVALS (ISI, IN ms)

|      | <i>Physical match</i> |                | <i>Name match</i> |                | <i>Different</i> |                |
|------|-----------------------|----------------|-------------------|----------------|------------------|----------------|
|      | <i>RT</i>             | <i>% error</i> | <i>RT</i>         | <i>% error</i> | <i>RT</i>        | <i>% error</i> |
| ISI  |                       |                |                   |                |                  |                |
| 0    | 1004                  | 10.0           | 1336              | 20.0           | 1305             | 0.0            |
| 700  | 1388                  | 0.0            | 1508              | 20.0           | 1532             | 0.0            |
| 1500 | 1392                  | 10.0           | 1554              | 0.0            | 1547             | 5.0            |

The number correct and the mean RTs (ms) for H.J.A., as a function of the type of match and the ISI, are given in Table 5.

The 'same' RT data were analysed in a  $2 \times 3$  analysis of variance, with the factors being type of match (physical vs name) and ISI (0, 700, 1500 ms), with each RT entered as a separate subject. There were reliable main effects of match type and ISI,  $F(2,48) = 9.49$  and  $F(1,48) = 10.52$ , both  $P < 0.001$ . The interaction was not significant,  $F(2,48) = 1.06$ ,  $P > 0.05$ .

H.J.A. shows a physical match advantage across the three ISIs used; in fact, the size of the advantage appears considerably larger than that normally found, presumably because of H.J.A.'s relatively slow letter identification times. The important finding here is that he seems able to maintain a visual code over at least 1500 ms, quite comparable with that found in normal subjects.

### *Summary*

H.J.A. does not appear impaired either in maintaining new visual information (Experiment 6) or in his stored memory for object shape (Experiment 8). However, there is some indication of an impairment of visual colour knowledge. The data support the interpretation that whilst there may be common mechanisms underlying colour perception and visual colour memory (both impaired in H.J.A.), the mechanisms of perceiving object structure and of memory for object structure seem to be separate (with only the former impaired in H.J.A.).

### *Section 5. Use of context*

To develop models of object recognition, it is crucial to understand how contextual information might be used to facilitate perceptual processing. A case such as H.J.A., who has intact semantic knowledge along with impaired perceptual

processing, provides a unique opportunity to examine whether contextual cues can help to override a perceptual deficit. Accordingly, H.J.A.'s use of contextual information was tested by examining his ability to match pictures and words and by examining the effects of a scene context on his object identification.

#### *Experiment 9. Picture-word matching*

Pictures were selected from the picture norms of Snodgrass and Vanderwart (1980). On each trial, 4 pictures were presented (in a  $2 \times 2$  format). They were either semantically related (e.g., shirt, coat, blouse, dress) or unrelated (e.g., hair, bed, car, rabbit). Pictures in the semantically related condition also tended to be visually similar. There were 20 trials in each condition. H.J.A. either read a word corresponding to the name of one of the pictures on a trial, or a name was read aloud to him (auditory presentation). He was asked to point to the picture corresponding to the word. The pictures were balanced over the test sessions in an ABBA design.

Given an auditory word prompt, H.J.A. scored 19/20 (95%) in the unrelated condition and 16/20 (80%) in the related condition. With a visual word prompt he scored 20/20 and 16/20 (80%) in the unrelated and related conditions respectively. Taking the data with auditory and visual word prompts together, he performed better in the unrelated than in the related condition (Fisher exact probability,  $P=0.013$ ).

H.J.A. is considerably better at matching pictures to words than he is at identifying the same pictures, indicating that he is able to make use of contextual information. Typically, he reported that when told the name of a picture he was able to retrieve a list of characteristic features of the object which he matched against the pictures. He made errors when there was a close overlap between the features of the target object and those of the distractor; thus confusing a tiger with a zebra, an owl with an eagle, a shirt with a coat, a violin with a guitar, etc. It should be noted that for at least some of the latter instances, he chose the distractor most visually similar to the target rather than another distractor which was either associated with the target or which showed at least as many semantic features (e.g., tiger and lion, shirt and tie, violin and piano). Such errors suggest that it is the visual, rather than the semantic, similarity of targets and distractors which primarily affects his performance.

#### *Experiment 10. Effects of a scene context*

The stimuli used were those described in Palmer (1975). They consisted of 20 line drawings of everyday objects normalized for size; 10 of the objects had a visually similar partner amongst the other 10 (e.g., car wheel—record; belt—watch). There were also 20 line drawings of contextual scenes (e.g., a car, a hand carrying a briefcase). Palmer found that such scenes facilitated the tachistoscopic identification of the target objects for normal subjects.

Each line drawing was either presented singly or paired with its matching scene, using an ABBA design across 2 testing sessions. H.J.A. was asked to name the

target object in both cases, and the context when it was shown. He named 5/20 (25%) of the line drawings correctly when they were shown in isolation and 14/20 (70%) correctly when they were shown alongside an appropriate context ( $\chi^2 = 6.42$ ,  $P < 0.01$ ). He identified 18/20 (90%) of the contextual scenes correctly (mis-identifying a house as a weighing machine and a bathroom as a workshop).

H.J.A. was better at identifying objects when paired with an appropriate context than when shown in isolation. This confirms that he can use semantic information to decide between alternative interpretations of visual input. However, context did not appear to alter his visual processing in any fundamental way; instead, it appeared to influence the responses assigned to the visual descriptions he derived. This is most clearly illustrated by his error responses to line drawings presented alongside a contextual scene. In one test session (conducted subsequently to Experiment 10), the scene context was given along with two visually similar line drawings, one of which was appropriate to the scene. H.J.A. was asked to point to the appropriate object and then to identify it. He made only 8/20 (40%) correct naming responses, which does not differ from his identification of the line drawings in isolation ( $\chi^2 = 1.0$ ). His naming errors reflected an interpretation of the object to fit the scene. For instance, when shown a garage scene and asked to choose between a telephone and a petrol pump, H.J.A. chose the telephone and identified it as an oil can.

### GENERAL DISCUSSION

We have documented the case of a patient, H.J.A., with a marked modality-specific deficit in visual object recognition. This deficit appears to be consequent on impaired perceptual processing. H.J.A.'s identification of both line drawings of objects and letters is strongly affected by their exposure duration (Experiment 3), he is relatively impaired at identifying overlapping figures (geometric shapes, letters and line drawings) when compared with when the same figures are shown in adjacent locations (Experiment 1), and he shows no evidence of having intact access to structural knowledge of objects from vision (in an object decision task; Experiment 2a). All of the above difficulties appear to be due to a problem in integrating local form information. For instance, his visual object identification is typically dependent on the use of independent (unintegrated) local feature descriptions, making performance very sensitive to the time available to encode the feature descriptions serially. A failure to integrate local part information with more global shape information will also impair the segmentation of overlapping figures and object decisions where the (meaningless) distractors contain local parts from real objects.

Nevertheless, H.J.A. performs at a high level on some perceptual tasks; he is well able to copy objects he fails to identify and he can match objects across at least some different views (Humphreys and Riddoch, 1984). Further, in contrast to normal subjects, H.J.A. is relatively good at making object decisions to silhouettes

(Experiment 2b). It is important to realize, though, that the perceptual tasks where H.J.A. performs relatively well have in common the property that they do not require integrated form descriptions. Copying may be carried out using local contour tracing and location marking routines (Ullman, 1984), different-view matching may be performed by comparing independent local-part descriptions across viewpoints, and object decisions using silhouettes may be based on undifferentiated global form information. None of the tasks may be considered diagnostic of normal perceptual representation (*see also* Levine, 1978).

With the exception of visual colour memory, H.J.A. appears to have good stored knowledge of objects. He has detailed semantic knowledge about the objects he cannot recognize (Experiments 4 and 5), he is able to draw the objects from memory (Experiment 6) and he can use context to facilitate identification performance (Experiments 9 and 10). Nor is his object recognition deficit due to a poor memory for visual material since he can maintain a visual code for at least 1500 ms (Experiment 8). Thus H.J.A.'s case seems to indicate the effects of a selective input processing deficit along with sparing of other aspects of the object recognition system.

*Implications for accounts of visual agnosia: defining integrative agnosia*

H.J.A. does not fit easily within the apperceptive-associative classification scheme typically applied to agnosic patients (e.g., Lissauer, 1890; Ratcliff and Newcombe, 1982). His marked visual recognition impairment coexists with accurate copying and good ability to match objects across some different viewpoints. The latter, preserved abilities, might be taken to confirm a diagnosis of associative agnosia (*see* Warrington, 1985). However, unlike at least some agnosics who have difficulty solely in associating perceptual with semantic information (e.g., Riddoch and Humphreys, 1987), H.J.A. appears to have an impaired perceptual representation of the visual world. Further, this perceptual impairment seems specifically to concern integrating local aspects of visual form and linking such information with global aspects of shape. H.J.A. does not have the deficits in processing local aspects of shape (such as contour tracing or orientation discrimination) documented in other patients classified as apperceptive agnosics (Benson and Greenberg, 1969; Campion, 1987).

We therefore propose that the classification scheme for visual agnosia needs to be expanded to accommodate H.J.A., and perhaps other cases which may be demonstrated as tests become more sensitive to the breakdowns which may occur in various substages of visual object recognition (*see* Humphreys and Riddoch, 1987). We suggest that the term integrative agnosia is a suitable description of H.J.A.'s specific problem in grouping local form information. Such a description may be appropriate for all patients with such a selective deficit along with intact discrimination of form elements. It follows that apperceptive and associative agnosia should be viewed solely as umbrella terms covering a number of distinct perceptual disorders.

H.J.A.'s deficit in grouping local form information impairs his visual object recognition. The impairment is not material-specific, and it affects the identification of letters and geometrical shapes as well as objects, given the appropriate presentation conditions. Indeed, it may be that, under normal viewing conditions, letters and geometrical shapes are often identified more easily than objects or line drawings because the former items are simpler and place fewer demands on the perceptual system; that is, in cases such as H.J.A., any effects of stimulus material may be better understood as reflecting quantitative parameters of a single recognition deficit rather than qualitative differences in the way different stimuli are handled. This account can also explain H.J.A.'s better identification of objects from classes with structurally distinct exemplars relative to classes with structurally similar exemplars (Section 1). The latter difference cannot be explained by positing a selective loss of stored visual knowledge for particular object classes (*see* Warrington and Shallice, 1984), since H.J.A. can draw from memory exemplars of the categories he finds difficult to recognize visually.

A second implication of the data concerns the argument that visual agnosia may be precipitated by an inability to identify more than one object at a time (i.e. simultanagnosia; Luria, 1959; Kinsbourne and Warrington, 1962). Since there is much evidence to suggest that we normally perceive only one object at a time (in the sense of being able to identify explicitly only one object amongst others concurrently available; Duncan, 1985; Humphreys, 1985), we presume that patients who appear particularly limited in this respect are deficient in switching attention between simultaneously available stimuli (i.e., they have a prolonged refractory period; *see* Levine and Calvanio, 1978). H.J.A.'s dependence on feature-by-feature descriptions for object recognition and the marked effects of exposure duration may be indicative of perceptual processes dependent on an abnormal refractory period. However, the refractory argument cannot provide a sufficient account of the data, since performance should then be normal when there is unlimited exposure time. This was clearly not the case. Further, if the argument were true, then the report of briefly reported stimuli should depend upon whether the stimuli are attended, and random errors should occur for those stimuli outside the focus of attention. We presume here that perceptual identification operates in an all-or-none fashion (*see* Humphreys, 1985). In contrast, H.J.A. made predominantly visually related errors, and this did not vary with the number of targets or the exposure duration (Tables 3 and 4; *see also* Pötzl, 1928; Ranschburg and Schill, 1932; Levine and Calvanio, 1978). Also, although H.J.A. finds two briefly presented letters more difficult to identify than one, his performance decreases to chance at about the same duration for the two conditions. There is little here to suggest qualitative differences between his performance with one and with two stimuli, and the data indicate that in both cases he is operating with partial visual descriptions when he fails to identify stimuli. There is also more direct evidence against the refractory argument, namely, that his RTs to nonoverlapping groups of 2 or 3 stimuli were relatively normal. If H.J.A. were impaired at switching attention we



would expect his RTs to be slow when he must attend to individual members of perceptual groups. It seems unlikely that H.J.A.'s feature-by-feature identification processes, vulnerable to the effects of exposure duration, are a function of impaired attentional processes operating on intact perceptual representations.

Other implications concern the relation between H.J.A. and other agnosic patients in the literature. For H.J.A., impaired processes in shape perception seem to coexist with intact stored knowledge of the structural characteristics of objects. This suggests that the deficits in stored structural knowledge of objects which seem to accompany early processing impairments in at least some agnosic patients should be considered as additional to the early processing deficits, which may in isolation produce impaired visual object recognition (e.g., Ratcliff and Newcombe, 1982). Similarly, patients with poor visual memory along with impaired perceptual processing seem to have an additional, and perhaps separate, impairment (e.g., Davidoff and Wilson, 1985).

In other cases, it has been argued that poor stored knowledge of objects is the primary cause of the agnosia (e.g., Warrington, 1975; Warrington and Shallice, 1984). One problem here is that the latter argument rests on an acceptance of the null hypothesis that perceptual processing is intact. A second problem concerns the grounds for arguing that a patient has degraded stored knowledge of stimuli rather than impaired input to that knowledge. Two pieces of evidence typically used for the latter purpose are the consistency of performance (where patients consistently fail on particular stimuli) and the demonstration of a hierarchical breakdown in the recognition process (where the patient shows preserved knowledge of general categorical information about an object relative to his or her knowledge of specific semantic attributes; *see* Warrington and Shallice, 1979, 1984; Shallice, 1987). Interestingly, H.J.A. shows both of the above patterns of performance; he consistently misidentifies certain objects while correctly identifying others and, for the objects he misidentifies, he demonstrates access to general rather than specific semantic knowledge from vision. However, there are good grounds for supposing that H.J.A. has intact stored knowledge about objects, given his drawings from memory and his good cued definition performance when the object's name is presented auditorily. Thus, although there may well be cases where poor stored knowledge of objects underlies visual agnosia, we should be cautious in arguing this only from evidence of a consistent hierarchical breakdown in recognition (*see also* Riddoch *et al.*, 1987).

### *Implications for theories of visual object recognition*

Visual object recognition is a complex process involving a number of distinct operations (*see* Marr, 1982). Recognition could therefore be impaired following disruption to any of these operations. We have proposed that H.J.A. is impaired at integrating local form description and that this impairment precipitates a wide range of perceptual difficulties. This suggests that at least one suboperation involves

grouping local form information together, and that this operation is distinct from that of deriving the local form descriptions. Brain damage can affect the former operation while leaving the latter intact.

H.J.A.'s case also demonstrates that at least some of the operations mediating perceptual processing are independent of those underlying our long-term memory of objects (*see* Allport, 1985). This appears to be true of form perception and memory but not perhaps of colour perception and memory.

Finally, we have shown that H.J.A.'s visual object identification is sensitive to the effects of context. However, context influenced H.J.A.'s assignment of responses to stimuli rather than his perceptual processing. Contextual input does not override an early deficit in the integration of visual form.

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## APPENDIX

The stimuli from categories with structurally distinct and structurally similar exemplars shown to H.J.A. in Experiment 5, their name frequencies, and whether or not H.J.A. correctly named the item on its first or second presentation.

*Objects from categories with structurally distinct exemplars*

|         |                  | Name<br>frequency<br>(occurrences<br>per million) | First<br>presentation | Second<br>presentation |
|---------|------------------|---------------------------------------------------|-----------------------|------------------------|
| Bicycle | (vehicle)        | 5                                                 | ✓                     | ✓                      |
| Bus     | (vehicle)        | 34                                                | ✓                     | ✓                      |
| Bed     | (furniture)      | 127                                               | ✓                     | ✓                      |
| Car     | (vehicle)        | 274                                               | ✓                     | ✓                      |
| Stool   | (furniture)      | 8                                                 | x                     | ✓                      |
| Table   | (furniture)      | 198                                               | ✓                     | ✓                      |
| Chair   | (furniture)      | 66                                                | ✓                     | ✓                      |
| Hammer  | (tool)           | 9                                                 | ✓                     | ✓                      |
| Pliers  | (tool)           | 1                                                 | ✓                     | ✓                      |
| Fork    | (household item) | 14                                                | ✓                     | ✓                      |
| Nail    | (tool)           | 6                                                 | ✓                     | ✓                      |
| Cup     | (household item) | 45                                                | ✓                     | ✓                      |

*Objects from categories with structurally similar exemplars*

|            |                  | <i>Name<br/>frequency<br/>(occurrences<br/>per million)</i> | <i>First<br/>presentation</i> | <i>Second<br/>presentation</i> |
|------------|------------------|-------------------------------------------------------------|-------------------------------|--------------------------------|
| Glass      | (household item) | 99                                                          | ✓                             | ✓                              |
| Saw        | (tool)           | 352                                                         | ×                             | ×                              |
| Hat        | (clothing)       | 56                                                          | ✓                             | ✓                              |
| Tie        | (clothing)       | 23                                                          | ×                             | ×                              |
| Coat       | (clothing)       | 43                                                          | ✓                             | ✓                              |
| Dress      | (clothing)       | 67                                                          | ×                             | ×                              |
| Sock       | (clothing)       | 4                                                           | ×                             | ×                              |
| Shirt      | (clothing)       | 27                                                          | ✓                             | ✓                              |
| Hair       | (body part)      | 148                                                         | ×                             | ×                              |
| Foot       | (body part)      | 70                                                          | ✓                             | ×                              |
| Nose       | (body part)      | 60                                                          | ×                             | ×                              |
| Finger     | (body part)      | 40                                                          | ×                             | ×                              |
| Leg        | (body part)      | 58                                                          | ×                             | ✓                              |
| Helicopter | (vehicle)        | 1                                                           | ×                             |                                |
| Train      | (vehicle)        | 82                                                          | ×                             |                                |
| Desk       | (furniture)      | 65                                                          | ✓                             |                                |
| Piano      | (furniture)      | 38                                                          | ✓                             |                                |
| Axe        | (tool)           | 12                                                          | ✓                             |                                |
| Knife      | (household item) | 76                                                          | ✓                             |                                |
| Spoon      | (household item) | 6                                                           | ✓                             |                                |
| Shoe       | (clothing)       | 14                                                          | ✓                             |                                |
| Skirt      | (clothing)       | 21                                                          | ×                             |                                |
| Glove      | (clothing)       | 9                                                           | ✓                             |                                |
| Cap        | (clothing)       | 27                                                          | ×                             |                                |
| Hand       | (body part)      | 431                                                         | ✓                             |                                |
| Arm        | (body part)      | 94                                                          | ✓                             |                                |
| Lips       | (body part)      | 69                                                          | ×                             |                                |
| Ear        | (body part)      | 29                                                          | ×                             |                                |
| Camel      | (animal)         | 1                                                           | ✓                             | ✓                              |
| Bear       | (animal)         | 57                                                          | ×                             | ×                              |
| Sheep      | (animal)         | 23                                                          | ×                             | ×                              |
| Chicken    | (bird)           | 37                                                          | ✓                             | ✓                              |
| Lion       | (animal)         | 17                                                          | ✓                             | ✓                              |
| Squirrel   | (animal)         | 1                                                           | ✓                             | ✓                              |
| Goat       | (animal)         | 6                                                           | ×                             | ×                              |
| Tiger      | (animal)         | 7                                                           | ×                             | ×                              |
| Bee        | (insect)         | 11                                                          | ×                             | ×                              |
| Butterfly  | (insect)         | 2                                                           | ✓                             | ×                              |
| Duck       | (bird)           | 9                                                           | ×                             | ✓                              |
| Mouse      | (animal)         | 10                                                          | ×                             | ×                              |
| Rabbit     | (animal)         | 11                                                          | ×                             | ×                              |
| Deer       | (animal)         | 13                                                          | ✓                             | ✓                              |
| Spider     | (insect)         | 2                                                           | ×                             | ×                              |
| Ant        | (insect)         | 6                                                           | ×                             | ×                              |
| Fox        | (animal)         | 13                                                          | ✓                             | ×                              |
| Eagle      | (bird)           | 5                                                           | ×                             | ×                              |
| Apple      | (fruit)          | 9                                                           | ✓                             | ✓                              |
| Pear       | (fruit)          | 6                                                           | ✓                             | ✓                              |
| Potato     | (vegetable)      | 15                                                          | ×                             | ×                              |
| Onion      | (vegetable)      | 15                                                          | ×                             | ×                              |
| Celery     | (vegetable)      | 4                                                           | ×                             | ×                              |
| Orange     | (fruit)          | 23                                                          | ×                             | ×                              |
| Lettuce    | (vegetable)      | —                                                           | ×                             | ×                              |
| Donkey     | (animal)         | 1                                                           | ×                             |                                |
| Zebra      | (animal)         | 1                                                           | ×                             |                                |
| Swan       | (bird)           | 3                                                           | ✓                             |                                |

*Objects from categories with structurally similar exemplars*

|             |             | <i>Name<br/>frequency<br/>(occurrences<br/>per million)</i> | <i>First<br/>presentation</i> | <i>Second<br/>presentation</i> |
|-------------|-------------|-------------------------------------------------------------|-------------------------------|--------------------------------|
| Owl         | (bird)      | 2                                                           | ×                             |                                |
| Cow         | (animal)    | 29                                                          | ✓                             |                                |
| Horse       | (animal)    | 117                                                         | ×                             |                                |
| Caterpillar | (insect)    | 1                                                           | ✓                             |                                |
| Lemon       | (fruit)     | 18                                                          | ×                             |                                |
| Carrot      | (vegetable) | 1                                                           | ×                             |                                |
| Banana      | (fruit)     | 4                                                           | ×                             |                                |

H.J.A.'s superior naming of objects from categories with structurally distinct exemplars relative to his naming of objects from categories with structurally similar exemplars, cannot easily be attributed to factors other than structural similarity. He shows no effects of name frequency on picture identification, so differences in name frequency between the categories cannot account for his performance. Also, his performance cannot be attributed to particular difficulties with animate objects or with objects whose individual names do not correspond to their 'base-level' representations (e.g., Rosch, 1975). Whereas most of the 'structurally distinct' items are inanimate, this classification does not hold for all the items (e.g., 'body parts' is a 'structurally distinct', animate category). Also, while some of the 'structurally similar' items have base-level representations corresponding to their category names (e.g., birds, insects), this does not hold for animals, fruits or vegetables.

# TRIGEMINAL SENSORY NEUROPATHY

## A STUDY OF 22 CASES

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### SUMMARY

The clinical and electrophysiological findings in 22 patients with chronic trigeminal sensory neuropathy are described. The main clinical feature was slowly evolving unilateral or bilateral facial numbness sometimes associated with pain and paraesthesiae and commonly with disturbed taste. Nine patients had either systemic sclerosis or mixed connective tissue disease. Of the 13 other patients, 9 had either organ or nonorgan specific serum autoantibodies. Blink reflex latencies were recorded in 17 patients, the commonest abnormality being an 'afferent' defect with modest prolongation of latency. Trigeminal sensory evoked responses were recorded in 14 cases, 6 showing mild prolongation of latencies. It is suggested that the lesion in this type of trigeminal neuropathy is in the trigeminal ganglion or in the proximal part of the main trigeminal divisions. This conclusion is supported by limited pathological data.

### INTRODUCTION

In 1959 Spillane and Wells described 16 cases of chronic trigeminal sensory neuropathy of unknown aetiology. Trigeminal sensory neuropathy was subsequently reported in association with a variety of connective tissue diseases: systemic lupus erythematosus (SLE) (Bailey *et al.*, 1956; Ashworth and Tait, 1971; Lundberg and Werner, 1972), Sjögren's or sicca syndromes (Kaltreider and Talal, 1969; Kennett and Harding, 1986), dermatomyositis (Ashworth and Tait, 1971), rheumatoid arthritis (Sokoloff and Bunim, 1957), and mixed connective tissue disease (MCTD) (Bennett *et al.*, 1978; Searles *et al.*, 1978; Lagarde and Lamotte-Barrillon, 1979; Vincent and Van Houzen, 1980). The most frequently reported association has, however, been with systemic sclerosis, first recognized two years before Spillane and Wells' description (Senseman, 1957). Gordon and Silverstein (1970), reviewing the neurological complications of systemic sclerosis, dismissed facial hypalgesia in 1 of the 130 patients as coincidental but two subsequent series established the strength of the association. Teasdall *et al.* (1980) reported 10 cases of systemic sclerosis with cranial nerve involvement, all including the trigeminal nerve. Farrell and Medsger (1982) noted 16 cases of trigeminal neuropathy among 442 patients

with systemic sclerosis and identified a further 25 cases in the literature. Several other authors have described trigeminal neuropathy with systemic sclerosis, mostly as single case reports (Beighton *et al.*, 1968; Ashworth and Tait, 1971; Casey and Lawton, 1971; Kabadi and Sinkoff, 1977; Edmondstone *et al.*, 1982; Lee *et al.*, 1984).

Two other types of trigeminal sensory disturbance warrant mention. Harris (1950) reported 5 cases with sudden onset of unilateral numbness, often with facial anaesthesia, in all three divisions with resolution but with the later development of trigeminal neuralgia. Some of these cases may have been due to brainstem demyelination. Blau *et al.* (1969) described 10 cases of acute trigeminal sensory neuropathy with partial or complete resolution. There were no other clinical features and the authors drew a parallel with Bell's palsy.

Direct pathological information on such cases is very limited and is derived from the few cases which have been explored surgically. Spillane and Wells (1959) and Ashworth and Tait (1971) favoured a lesion in the trigeminal ganglion or sensory root. Teasdall *et al.* (1980), on clinical grounds, argued in favour of a peripheral rather than proximal lesion, suggesting that a combination of microangiopathy and fibrosis might be responsible for the trigeminal lesions in systemic sclerosis. There is, of course, no particular reason to assume a common site or pathological process for the different types of trigeminal neuropathy.

The present work is a clinical and electrophysiological study of 22 patients with trigeminal sensory neuropathy encountered by the authors between 1975 and 1985. The patients fall into two groups. The first had either systemic sclerosis or mixed connective tissue disease. In the second group, although there was no clinical evidence of active connective tissue disorder, there was an increased incidence of autoimmune disease and a high incidence of serum organ-specific and nonorgan-specific autoantibodies. A preliminary report has already appeared (Lecky *et al.*, 1986).

#### PATIENTS AND METHODS

All 22 patients were examined personally by the authors. Cases 1-6 met American Rheumatism Association criteria for 'definite' systemic sclerosis (Masi *et al.*, 1979; American Rheumatism Association Diagnostic and Therapeutic Criteria Committee, Subcommittee for Scleroderma Criteria, 1980). Cases 7-9 were classified as the 'overlap syndrome' of mixed connective tissue disease (MCTD) (Sharp *et al.*, 1972) which is characterized clinically by a combination of features similar to those found in SLE, systemic sclerosis and polymyositis and serologically by the presence of antibody to extractable nuclear antigen (ENA). Although ENA was not estimated in Case 8, this was classified as MCTD because of the past history of arthritis.

All patients underwent full general medical and neurological examination. Trigeminal sensation was tested in all three divisions for pain, temperature and light touch. Pain sensation was also tested on the anterior part of the tongue and within the oral cavity. Taste was tested on the anterior tongue with either four standard test substances (sucrose, sodium chloride, quinine sulphate and citric acid) and/or by the application of effervescent ascorbic acid tablets to the tongue. Taste was noted as being either absent or impaired. Impairment was defined as either failure to detect either the ascorbic acid



TABLE 1. CLINICAL DETAILS

| Case | Age<br>(yrs) | Sex | Duration<br>(yrs) | Symptoms                          | Distribution |    |    |       |    |    | Taste |
|------|--------------|-----|-------------------|-----------------------------------|--------------|----|----|-------|----|----|-------|
|      |              |     |                   |                                   | (R)V1        | V2 | V3 | (L)V1 | V2 | V3 |       |
| 1    | 67           | F   | 14                | Electric shocks                   | +            | +  | +  | +     | +  | +  | a     |
| 2    | 56           | F   | 3                 | Numbness                          | -            | -  | -  | +     | +  | +  | s     |
| 3    | 48           | F   | 15                | Numbness (incidental finding)     | +            | -  | -  | +     | -  | -  | a     |
| 4    | 70           | F   | 13†               | Numbness, pain                    | -            | +  | +  | +     | +  | +  | n.t.  |
| 5    | 69           | M   | 3                 | Numbness, pain                    | -            | -  | -  | +     | +  | +  | s     |
| 6    | 46           | F   | 4                 | Aching, numbness, dysaesthesia    | +            | +  | +  | +     | +  | +  | s     |
| 7    | 48           | M   | 3                 | Numbness                          | +            | +  | +  | +     | +  | +  | a     |
| 8    | 55           | F   | 15†               | Sore tongue, burning cheeks       | -            | +  | +  | +     | +  | +  | n.t.  |
| 9    | 54           | M   | 6                 | Paraesthesiae, numbness           | -            | +  | +  | -     | +  | +  | s     |
| 10   | 64           | F   | 3                 | Altered sensation                 | -            | -  | -  | +     | +  | -  | n     |
| 11   | 57           | F   | 8                 | Numbness                          | +            | +  | +  | -     | -  | -  | s     |
| 12   | 76           | F   | 10                | Electric shocks, numbness         | -            | +  | +  | -     | +  | +  | n     |
| 13   | 51           | F   | 1                 | Pain, numbness                    | ?            | +  | +  | -     | -  | -  | a     |
| 14   | 53           | F   | 13                | Pain, numbness                    | +            | +  | +  | -     | -  | -  | s     |
| 15   | 63           | M   | 2                 | Tingling, numbness                | +            | +  | +  | +     | +  | +  | s     |
| 16   | 70           | F   | 1                 | Numbness, soreness                | -            | +  | +  | -     | +  | +  | s     |
| 17   | 47           | M   | 2                 | Numbness                          | +            | +  | +  | -     | -  | -  | a     |
| 18   | 48           | F   | 2                 | Paraesthesiae, numbness, soreness | +            | +  | +  | +     | +  | +  | s     |
| 19   | 43           | F   | 6                 | Pain, numbness                    | ?            | +  | +  | -     | -  | -  | n     |
| 20   | 47           | F   | 9                 | Pain, burning, numbness           | ?            | +  | +  | -     | -  | -  | a     |
| 21   | 34           | F   | 1                 | Itching, numbness                 | -            | +  | +  | -     | +  | +  | n     |
| 22   | 26           | M   | 1                 | Numbness, burning                 | -            | ?  | ?  | -     | +  | +  | n     |

† Died. Involvement: - = normal sensation; + = abnormal; ? = symptoms without abnormal signs. Taste: n = normal; a = asymptomatic abnormality; s = symptomatic abnormality; n.t. not tested.

or two of the other substances, or a clear discrepancy between the two sides. Clinical details are summarized in Table 1.

In addition to standard haematology, biochemistry and radiology for diagnostic purposes, all patients had detailed serum autoantibody studies performed. Thyroglobulin and thyroid microsomal antibodies were assayed by standard haemagglutination techniques. Antinuclear, gastric parietal cell, smooth muscle and mitochondrial antibodies were determined by indirect immunofluorescence with rat stomach, liver and kidney tissue as substrate. Titres greater than 1:10 were considered positive. Antinative double stranded DNA (dsDNA) antibody was determined either by indirect immunofluorescence with Crithidia as substrate or by haemagglutination. For comparison, the incidence of these autoantibodies was determined in 320 neurological inpatients and outpatients at The National Hospitals in whom antibody screening had been requested. These cases were taken from a sequence of laboratory requests selected to match the patients of the study for age range and sex ratio. The incidence of autoantibodies in Cases 10-22 was compared with that in the controls using Fisher's Exact Test (two-tailed).

Blink reflex latencies to supraorbital nerve stimulation were recorded with a fine concentric needle electrode in orbicularis oculi using a Medelec MS6 Electromyograph (after Kimura, 1983). The stimuli were 0.1 ms square wave impulses delivered singly at 0.5 Hz through surface electrodes at the supraorbital notch. A minimum of 10 stimuli were delivered and the shortest reproducible latency was measured. Reflex latencies evoked by infraorbital nerve stimulation were found to be inconsistent and were not used.

Trigeminal somatosensory evoked potentials (TSEPs) were recorded with scalp electrodes during stimulation of individual maxillary (V2) and mandibular (V3) branches of the trigeminal nerves. The stimuli were 0.05 ms square wave impulses delivered at 2 Hz with an amplitude 2 to 4 times greater than the sensory threshold through silver disc electrodes. For maxillary branch stimulation the cathode was placed just above the upper lip near the corner of the mouth with the anode 1 to 2 cm

lateral and slightly superior. The cathode was placed just below the lower lip at the angle of the mouth for mandibular nerve stimulation with the anode 1 to 2 cm inferior and slightly lateral. Recording electrodes were Ag/AgCl discs fixed over the face area of the contralateral somatosensory cortex (C5/6) referred to a midfrontal electrode (Fz, International 10–20 System). A negative potential at the active electrode produced an upward deflection. The EEG was sampled and averaged for 50 ms after each stimulus (time constant 300 ms ( $-3$  dB), high frequency filter 1 kHz) and at least two runs of 256 responses were averaged for each nerve separately to ensure reproducibility. A display oscilloscope allowed assessment of artefact and EMG activity. Normative data were obtained from 14 healthy control subjects. Absolute latencies or differences between each side greater than 2.5 SD above the mean were defined as abnormal.

In Case 15, a biopsy of the right supraorbital nerve was obtained at the level of the supraorbital notch and processed for light and electron microscopy.

## CASE REPORTS

### *Case 1*

Female, aged 67 yrs, systemic sclerosis. In 1970 she had noted the gradual onset of abnormal sensation over the whole right side of the face with identical symptoms occurring on the left in the following year. Contact of the face with sharp objects elicited an electric shock-like sensation and appreciation of temperature was impaired. At about the same time she developed Raynaud's phenomenon, dysphagia and difficulty in extending the fingers. Two years after the onset of these symptoms she was found to have bilateral impairment of light touch and temperature sensation, and dysaesthesia to pin prick in all three trigeminal divisions. There was mild proximal limb weakness. There was proximal and distal scleroderma with mild painful limitation of passive elbow and shoulder movement. Her neurological symptoms did not respond either to carbamazepine 800 mg daily or prednisolone 40 mg on alternate days. When seen in 1984 she reported that the facial discomfort was less but that the numbness now included the tongue. She complained of indistinct speech and a tendency to dribble. Examination showed hypalgesia in all trigeminal divisions bilaterally, including the anterior tongue, with the first division most severely affected. Light touch was impaired in V1. Temperature sensation was normal. The corneal reflexes were normal. Taste was impaired over the anterior tongue.

### *Case 2*

Female, aged 56 yrs, systemic sclerosis. Eight years previously she had developed Raynaud's phenomenon and hypertension. After 5 yrs she noted left circumoral numbness which extended over several months to include the whole left face. The inside of the left cheek was numb and taste was impaired on the left. Chewing food on the left side was difficult. One year after the onset of numbness there was impairment of touch, pain and temperature sensation in all three left trigeminal divisions with a depressed left corneal reflex. Taste was impaired over the left side of the tongue. There was scleroderma of face, upper trunk and hands.

She subsequently reported worsening of the numbness and extension to include the left gums and left side of the tongue. In 1984 there was analgesia in left V2 with hypalgesia in V1 and V3 including the tongue. Light touch was impaired in all three divisions and the left corneal reflex was decreased. Taste was impaired on the left side of the tongue.

### *Case 3*

Female, aged 48 yrs, systemic sclerosis. For 20 yrs she had had Raynaud's phenomenon affecting all four extremities. After 15 yrs she developed dysphagia and swelling of the extremities. At this time she was noted to have the features of CRST (calcinosis, Raynaud's, sclerodactyly, telangiectasia).

a variant of systemic sclerosis. An incidental finding was anaesthesia in V1 bilaterally and loss of the corneal reflexes.

When seen in 1984 she reported that there had been no change in her sensory deficit which consisted of numbness of the forehead and the bridge of the nose, especially in cold weather. The neurological abnormalities were unchanged. Despite normal primary sensation in the second and third divisions, taste was impaired on both sides of the tongue.

#### *Case 4*

Female, died aged 70 yrs, systemic sclerosis. Raynaud's phenomenon developed in childhood and became severe at age 54 yrs. The next year she developed numbness of the left cheek associated with a constant ache and stabbing pains precipitated by washing, chewing or exposure to cold wind. Two years later she was noted to have impairment to pin prick in all three divisions on the left and in the perioral region on the right. The corneal reflexes were depressed. Scleroderma of face and hands was evident. The facial pain did not respond to carbamazepine but subsequently became less troublesome. She developed severe pain in the extremities requiring morphine. She died after developing peripheral gangrene and cardiac failure. Autopsy was not performed.

#### *Case 5*

Male, aged 69 yrs, systemic sclerosis. Four years previously he had developed Raynaud's phenomenon and pain and stiffness of the shoulders and fingers. Nine months later numbness 'like a dental anaesthetic' started at the angle of the mouth on the left and extended over several weeks to involve the whole left side of the face and the left half of the tongue. He noticed a scalding sensation, especially on cold exposure, and a spontaneous lancinating pain in the left cheek occurring several times daily. The pain and discomfort became less prominent and the sensory deficit remained static. Taste was described as 'dull'. There was impairment to all three sensory modalities in the whole left trigeminal territory maximal in V2. The left corneal reflex was impaired. Taste was impaired on the left. There was mild bilateral sensorineural deafness.

#### *Case 6*

Female, aged 46 yrs, systemic sclerosis. She had suffered from Raynaud's phenomenon since childhood. Five years previously she developed pain and stiffness of the hands. Pains in the hands were relieved by bilateral carpal tunnel decompression although nerve conduction studies were not performed. The next year she awoke with aching in the left lower jaw which gradually spread over the cheek, and the face felt numb and stiff. Similar symptoms occurred on the right the following year. Exposure to wind produced an unpleasant itching and tingling and facial contact with bedclothes or face flannel caused discomfort. There was no response to carbamazepine. The discomfort improved but the numbness became more intense, especially around the mouth, and extended to the forehead. The gums became sore, there was difficulty chewing on the right, speech became slightly indistinct, and taste was impaired on the right. Scleroderma of the face and hands became evident. In 1984 she considered her symptoms to be static. There was loss to pain and temperature with impaired light touch in all three divisions on the right with impaired pain and temperature on the left where light touch was preserved. There was hypalgesia over the anterior tongue and taste was impaired on the right. The right corneal reflex was diminished.

#### *Case 7*

Male, aged 48 yrs, MCTD. Three years previously a right upper canine tooth was extracted. He felt that right facial sensation never fully recovered from the local anaesthetic. Over the next few months numbness gradually extended over the whole face. He noted impaired appreciation of temperature over the face. The severity of numbness did not alter but he became aware of painful

itching of the face, oral discomfort and nonspecific difficulty on prolonged talking. There was also a 3 yr history of Raynaud's phenomenon. When seen 2 yrs after onset there was patchy bilateral impairment of pain and temperature sensation in all three divisions with normal corneal reflexes. Taste was also bilaterally impaired. There was tightening of the skin over the nose and around the mouth. Chest x-ray showed basal fibrosis and barium swallow revealed disordered oesophageal motility. He was found to be hypothyroid. The facial discomfort did not respond to carbamazepine.

#### *Case 8*

Female, died aged 55 yrs, MCTD. When aged 38 yrs, rheumatoid arthritis was diagnosed. Six months later she developed Raynaud's phenomenon and tingling and soreness of both sides of the tongue, exacerbated by hot or cold. There followed numbness of the left cheek gradually extending to the left side of the lips and forehead. The cheek had a burning sensation and the angle of the mouth felt as if scalded. Examination showed hypalgesia in left V1 and anaesthesia in V2 and V3 with a normal corneal reflex. Treatment with oral prednisolone was without effect. Two years later numbness extended to the right V2 and V3. At the age of 49 yrs she developed dyspnoea and chest pain. She was noted to have scleroderma of the face, hands and feet. Digital ischaemia was temporarily improved by bilateral cervical sympathectomy. The facial sensory loss did not alter. She subsequently developed dysphagia. She died at the age of 55 of myocardial infarction and bronchopneumonia. Macroscopic examination of the brain showed oedema of the meninges only. The trigeminal ganglia and nerves were not examined.

#### *Case 9*

Female, aged 54 yrs, MCTD. Seven years previously she had developed Raynaud's phenomenon. The next year widespread joint and muscle pains occurred. She noted paraesthesiae and numbness of the right upper lip which gradually extended over the whole right lower face and then to the left lower face and which included gums, palate and tongue. Foods had a spurious salty taste. This improved with some residual dysgeusia.

She was found to have scleroderma of the hands. Muscle biopsy, elevated serum creatine kinase activity and EMG studies indicated polymyositis. The facial sensory symptoms became confined to the circumoral region. Speech became indistinct and there was a tendency to dribble. Treatment with carbamazepine and oral corticosteroids did not affect the sensory symptoms. In 1984 the first trigeminal divisions were clinically normal. There was bilateral dysaesthesia to pin prick in V2 and V3 with normal light touch and temperature sensation and corneal reflexes. The anterior part of the tongue was anaesthetic. Taste was impaired. There was mild proximal limb weakness.

#### *Case 10*

Female, aged 64 yrs. She had developed rheumatoid arthritis 25 yrs previously and was treated with oral corticosteroids and gold injections. Three years previously she noted abnormal sensation over the left forehead, cheek and pinna. There was initial progression but after a year, symptoms became confined to the forehead. Examination showed no active arthritis. Pain and temperature sensation and light touch were impaired in left V1 and temperature sensation was impaired in V2. The left corneal reflex was decreased.

#### *Case 11*

Female, aged 57 yrs. Eight years previously she had developed numbness of the right lower lip followed by soreness and tingling of the lip and the right side of the tongue. When first seen she was noted to have sensory impairment in the territory of the right lingual and inferior dental nerves with sparing of the auriculotemporal nerve. There was mild wasting of the right masseter and the right lateral pterygoid was weak. The extent of the trigeminal sensory impairment increased and 2 yrs later

included the whole of the first and second divisions. She had also developed alopecia areata and benign paroxysmal positional vertigo. In 1984 there was impairment to pin prick in the right first division and loss to pin prick, temperature and light touch in the second and third divisions. The corneal reflexes were equal. Taste was impaired over the right half of the tongue. Mild wasting of the right masseter persisted.

#### *Case 12*

Female, aged 76 yrs. Eleven years previously she underwent excision of a mucoid carcinoma of the breast. Eight years previously she received radiotherapy to the breast for a small local recurrence. Investigation at this time, and subsequently, showed no evidence of metastatic disease. Ten years previously she had developed left circumoral numbness with a pricking sensation like 'repeated electric shocks'. The numbness spread over the whole left face over a period over about 5 months. Examination at this time showed impairment to pin prick in all three divisions and a decreased corneal reflex on the left. There was also right conductive deafness. Her symptoms then remained static except for the development of a moderate left sensorineural deafness. The facial discomfort responded neither to carbamazepine nor to phenytoin. One year previously she complained of similar but milder right facial symptoms but no new signs were found. The right-sided symptoms then resolved and those on the left remained unchanged. She mentioned difficulty chewing which she attributed to disturbed sensation. In 1984 examination of the first divisions and the corneal reflexes was normal. There was subjective impairment to all three sensory modalities in V2 and V3 bilaterally especially on the left. The deafness was as before. There was no sign of carcinoma.

#### *Case 13*

Female, aged 51 yrs. Four months before she was first seen she developed an intermittent pricking sensation at the right nasolabial fold. After 4 wks. discomfort became more severe and extensive involving the right forehead and cheek 'as if a hand was gripping the cheek'. She became aware of right facial numbness which persisted although the discomfort improved. There was hypalgesia in right V2 and V3 including the right half of the tongue and with impairment of taste over the right half of the tongue anteriorly. The corneal reflexes were normal. One year later the signs had not changed.

#### *Case 14*

Female, aged 53 yrs. Thirteen years previously she had developed pain in the right lower gum which resolved after 1 wk to be replaced by numbness of the right lower lip slowly extending to involve the right lower face and the right half of the tongue. One month later there was anaesthesia in the right third division. After 5 months the second division was similarly involved. She was aware of impaired taste on the right side of the tongue and discomfort of the right side of the face especially in warm weather. All her symptoms remained unchanged. In 1984 there was almost complete anaesthesia in all three divisions on the right side with a decreased right corneal reflex. Taste was impaired on the right anterior aspect of the tongue.

#### *Case 15*

Male, aged 63 yrs. Two years previously a left maxillary dental abscess was treated with antibiotics. Shortly afterwards he developed numbness over the right upper lip which extended over a period of months to involve the inner and outer aspect of both cheeks, tongue and lips. After a year his entire face was anaesthetic. The initial symptoms were associated with transient facial tingling. He noted impaired taste. There was difficulty in chewing and swallowing, probably secondary to the sensory loss, such that he preferred to take semisolids. Speech became indistinct. Examination shortly after onset showed numerous nasal polyps and a right oroantral fistula. This was closed and a right Caldwell-Luc operation was performed. There was no histological evidence of malignancy and

subsequent oral examination has been satisfactory. Eight months after onset he developed bilateral keratitis resulting in corneal scarring. He was fitted with soft contact lenses and a right tarsorrhaphy was performed. General examination was normal except for poor dentition. Visual acuities were 6/60 right and 6/9 left. There was marked right corneal scarring with cataract and posterior synechiae. Both trigeminal territories were anaesthetic except for slight residual appreciation of light touch in the lower face. The corneal reflexes were absent. There was mild bilateral sensorineural deafness probably due to occupational noise exposure. The knee and ankle reflexes were absent but there was no other abnormality in the limbs. The right supraorbital nerve was biopsied (*see below*). Nerve conduction studies showed no evidence of a generalized peripheral neuropathy.

#### *Case 16*

Female, aged 70 yrs. Nine months previously she had noted numbness of the left upper lip and cheek described as being like a dental anaesthetic. The numbness subsequently extended to the left side of the nose, the left lower eyelid and the left side of the tongue and was associated with soreness. About 6 months later she developed numbness of the right cheek and lips. Her eyes itched. She noted impairment of taste, commenting that food felt and tasted like flour. There was a 4 month history of Raynaud's phenomenon. Examination showed bilateral hypalgesia and dysaesthesia in V2 and V3, more severe on the left. Temperature sensation was subjectively altered but light touch was unimpaired. The first divisions and the corneal reflexes were normal. Taste was impaired over the left side of the tongue.

#### *Case 17*

Male, aged 47 yrs. Eighteen months previously he received a local anaesthetic for right lower dental work. About 6 months later numbness of the right upper and lower lips developed. The numbness extended to the angle of the jaw and included the gums and the right half of the tongue which felt 'wedge shaped'. Taste was unaffected. Previous investigation had shown mild elevation of hepatic transaminases and a liver biopsy was consistent with chronic active hepatitis. Autoantibodies were, however, negative and the histological abnormality was felt also to be consistent with ketoconazole-induced hepatitis, a drug taken by the patient for fungal nail infection. Examination showed hypalgesia in the whole right trigeminal territory. Cotton wool elicited itching dysaesthesia. Temperature sensation and the corneal reflexes were normal. Taste was impaired. The rest of the neurological examination was normal except for an equivocal right plantar response.

#### *Case 18*

Female, aged 47 yrs. This West Indian patient gave a 5 yr history of Raynaud's phenomenon. Two years previously she had developed numbness of the right cheek and at the angle of the mouth which gradually extended to the whole right face and then to the left face. The numbness was associated with soreness and paraesthesiae of the face which felt 'fat'. She reported difficulty chewing and speaking clearly. Taste was initially severely impaired but later improved. Soon after the onset of numbness she was noted to have a facial 'butterfly' rash and alopecia. ANA was elevated but DNA binding was normal. Corticosteroid treatment was associated with psychosis for which phenothiazines were given. Neither steroids nor carbamazepine influenced her facial sensory symptoms. There was subjective impairment to all sensory modalities in the whole of both trigeminal territories. V2 was more severely involved and here two-point discrimination was greater than 3 cm. The tongue was almost anaesthetic. Both corneal reflexes were depressed. There were almost continuous choreiform movements of both sides of the face which at times the patient would attempt to arrest with her hands. She had difficulty in protruding her tongue commenting that she could not feel where it was. Speech was slow and mildly dysarthric. The rest of the neurological examination was normal.

*Case 19*

Female, aged 43 yrs. Six years previously she developed pain in the right side of the throat which resolved. Shortly afterwards she was aware of brief spontaneous shooting pains over the right cheek. About 3 yrs later the right cheek and lips became numb although the pains resolved. Numbness gradually extended to the right half of the tongue, the right gums and then the whole right lower face. One year later numbness of the right forehead became apparent when she plucked her eyebrow. The sensory loss above the eye later resolved but the lower facial numbness became denser. She also noted slight right-sided deafness. Right V1 was normal. There was severe impairment to all modalities in right V2 and V3 including the gums and the right half of the tongue. The corneal reflexes were normal. There was 30 dB high tone sensorineural deafness on the right which neuro-otological assessment suggested to be of cochlear origin.

*Case 20*

Female, aged 47 yrs. Nine years previously she developed episodic left frontal pains which remitted but which recurred 2 yrs later and which were then associated with a burning ache over the left lower face. The burning sensation became less severe after 3 wks. Four days after it began she noted progressive numbness over the left cheek beginning at the nasolabial fold and at the angle of the mouth. Numbness and residual discomfort persisted. Examination showed loss of pain and temperature sensation in infraorbital nerve distribution with less severe impairment over the rest of left V2 and V3 including the hard palate, gums and cheek. The corneal reflexes were normal. Taste was impaired over the left side of the tongue.

*Case 21*

Female, aged 35 yrs. There was a 2 yr history of Raynaud's phenomenon. Two years previously she had developed episodic pain in the region of the lower wisdom teeth and at least two episodes of gum or dental sepsis requiring antibiotic treatment. Both lower wisdom teeth were extracted under local anaesthesia 1 yr later and this pain did not recur. About 3 months before the dental extractions she developed numbness of the left upper lip spreading to include the whole left lower face which was associated with itching and paraesthesiae. Ten months later she developed similar symptoms over the right lower face and noted numbness of the tongue. Prompt corticosteroid treatment at the onset of the right-sided symptoms did not prevent their evolution. Examination showed subjective alteration to all sensory modalities in V2 and V3 bilaterally. The corneal reflexes were normal.

*Case 22*

Male, aged 24 yrs. Fourteen months previously he developed numbness over the left forehead. One week later he became aware of more extensive numbness over the left cheek, jaw and lips. This fluctuated but persisted. Shaving or exposure to cold produced an unpleasant burning sensation over the cheek. One month previously he awoke with similar symptoms over the right cheek which resolved after a few days except for some residual tingling. There was subjective alteration to all modalities in left V2 and V3 including the left side of the hard palate and tongue with normal corneal reflexes. Right trigeminal sensation and taste were normal.

## RESULTS

*Routine haematology*

Routine haematological and biochemical tests were normal except for mild elevation of the ESR in some of the systemic sclerosis group. Serology for syphilis was negative. In Case 12, serum vitamin B<sub>12</sub> was 60 mg/ml (normal 200–400) and part I Schilling test was 2.5% (normal 10–30%).

### *Radiology*

Chest x-rays were normal except for basal fibrosis in 4 of the patients with systemic sclerosis. Five of these patients also had disordered oesophageal motility on barium swallow. No abnormality was found on skull x-ray. CT head scans in 13 patients showed no abnormality other than mild cerebral atrophy in Cases 5, 10 and 12.

### *Cerebrospinal fluid*

The CSF was examined in 9 patients and was normal in 7. Case 8 had a mildly elevated total protein content (0.8 g/l) and Case 14 had 8 lymphocytes/ $\mu$ l with normal total protein. In 6 cases either CSF IgG/albumin ratio was estimated or CSF protein electrophoresis was carried out and no significant abnormality was found.

### *Autoantibody studies*

The results of serum autoantibody estimations are given in Table 2.

The high incidence of ANA in the systemic sclerosis/MCTD group was not unexpected. Among the 13 other patients a high incidence of both ANA and other autoantibodies was also found. In Cases 10–22, ANA was found in 62% in titre  $>1:10$  and in 23% in titre  $>1:80$  (neurological control group 20% and 3%, respectively). For both titres the differences were significant ( $P=0.003$  and  $P=0.02$ , respectively). Lennon *et al.* (1982) found either ANA or rheumatoid factor in 15% of neurological patients and Tunbridge *et al.* (1977) found ANA in approximately 3% of a normal adult population. A positive titre of dsDNA was found in only 1 case. ENA, a marker for MCTD (Sharp *et al.*, 1972), was found only in patients with this diagnosis.

The incidence of other antibodies was as follows (neurological controls in brackets): smooth muscle 15% (3%); mitochondrial 8% (1%); thyroglobulin 8% (7%); thyroid microsomal 31% (11%,  $P=0.1$ ); gastric parietal cell 31% (5%,  $P=0.02$ ). The incidence in the neurological controls is similar to that found by Lennon *et al.* For comparison, the population study of Tunbridge *et al.* gave the following incidence: smooth muscle 1.5%; mitochondrial 0.5%; thyroglobulin 2% and thyroid microsomal 5%. Excluding ANA, less than 5% of the neurological controls had positive titres of two autoantibodies and none more than two, whereas among Cases 10–22, 31% had two, and 23% more than two, positive titres.

### *Electrophysiology*

In 17 of the 22 cases recordings were made of the blink reflex latencies evoked by supraorbital nerve stimulation. In this reflex there is an early unilateral, R1, response at about 10 ms mediated by a unilateral pontine arc. The later bilateral, R2, response at about 30 ms involves a more complex pathway in the pons and lateral medulla (Kimura, 1983).



TABLE 2. SERUM AUTOANTIBODY TITRES

| Case | ANA      | dsDNA | ENA/RNP | TM | TGA | SM | GPC | MCA | RhF |
|------|----------|-------|---------|----|-----|----|-----|-----|-----|
| 1    | 1:2560   | —     | —       | +  | —   | —  | +   | —   | —   |
| 2    | 1:640    | —     | —       | —  | —   | —  | —   | —   | —   |
| 3    | 1:160    | —     | —       | +  | —   | —  | —   | —   | —   |
| 4    | +        | —     | n.d.    | —  | —   | —  | —   | —   | +   |
| 5    | 1:80     | 1:80  | n.d.    | —  | —   | —  | —   | —   | +   |
| 6    | —        | —     | —       | —  | —   | —  | —   | —   | —   |
| 7    | > 1:1280 | —     | +       | +  | —   | —  | +   | —   | +   |
| 8    | > 1:160  | n.d.  | n.d.    | —  | —   | —  | —   | —   | —   |
| 9    | 1:320    | —     | +       | —  | —   | —  | —   | —   | +   |
| 10   | —        | —     | —       | —  | —   | —  | —   | —   | —   |
| 11   | 1:10     | —     | —       | +  | —   | +  | +   | —   | —   |
| 12   | 1:40     | —     | —       | +  | —   | —  | +   | +   | —   |
| 13   | —        | —     | —       | —  | —   | —  | —   | —   | —   |
| 14   | —        | —     | —       | +  | +   | —  | +   | —   | —   |
| 15   | 1:80     | —     | —       | —  | —   | —  | —   | —   | —   |
| 16   | 1:10     | —     | —       | —  | —   | —  | —   | —   | —   |
| 17   | —        | —     | —       | —  | —   | —  | —   | —   | —   |
| 18   | 1:2560   | —     | —       | —  | —   | —  | —   | —   | —   |
| 19   | 1:10     | —     | —       | +  | —   | —  | —   | —   | —   |
| 20   | 1:10     | —     | —       | —  | —   | +  | +   | —   | —   |
| 21   | 1:640    | —     | —       | —  | —   | —  | —   | —   | —   |
| 22   | —        | —     | —       | —  | —   | —  | —   | —   | —   |

ANA = antinuclear antibody; dsDNA = anti-double stranded DNA; ENA = extractable nuclear antigen; RNP = ribonuclear protein; TM = thyroid microsomal; TGA = thyroglobulin; SM = smooth muscle; GPC = gastric parietal cell; MCA = mitochondrial; RhF = rheumatoid factor; n.d. = not done.

In 6 patients (Table 3) latencies were normal. Two patients with severe sensory loss in the first division (Cases 6, 15) showed no response on stimulation of the affected side(s). Case 1 showed absent R1 with normal R2 which, Kimura (1983) implies, may not be abnormal using single shock stimuli. Two cases (10, 18) showed nonspecific abnormalities (delay in ipsilateral R2 and absent R2, respectively) of uncertain significance. The most common abnormality, found in 6 cases, was an 'afferent' defect, that is, delay in all components but with normal latencies on stimulating the contralateral supraorbital nerve. The prolongation of R1 latencies in these cases was modest. Only one recording (Case 20) showed absolute prolongation of R1 greater than 1.0 ms and in 3 cases the abnormality was relative rather than absolute.

Trigeminal sensory evoked potentials (Table 4) were normal in 6 cases. No response was obtained in Case 15 (blink reflex also absent). Two patients had degraded responses and 5 had prolonged latencies. In 2 of these (Cases 2, 6) the abnormalities correlated with blink reflex prolongation.

#### *Supraorbital nerve biopsy*

The supraorbital nerve from a patient (Case 15) with almost complete trigeminal anaesthesia showed a severe loss of myelinated fibres (fig. 1). The supraorbital nerve obtained at autopsy from a neurologically normal control of the same age

TABLE 3. BLINK REFLEX RECORDINGS

| Blink reflex latencies (ms) |               |       |     |     |      |     |     |               |
|-----------------------------|---------------|-------|-----|-----|------|-----|-----|---------------|
|                             |               | Right |     |     | Left |     |     |               |
| Case                        | Side involved | R1    | R2i | R2c | R1   | R2i | R2c | Comment       |
| 1                           | R, L          | —     | 40  | 40  | —    | 40  | 242 | Absent R1     |
| 2                           | L             | 11    | 35  | 35  | 13.5 | 37  | 45  | L afferent    |
| 3                           | R, L          | 10    | 38  | 38  | 10   | 40  | 40  | Normal        |
| 6                           | R, L          | —     | —   | —   | 11   | 33  | 35  | R absent      |
| 7                           | R, L          | 11    | 35  | 35  | 12   | 36  | 36  | Normal        |
| 9                           | R, L          | 11    | 30  | 33  | 12   | 31  | 32  | Normal        |
| 10                          | L             | 11.5  | 33  | 42  | 11.5 | 243 | 32  | Delayed L R2i |
| 11                          | R             | 13    | 50  | 50  | 10   | 40  | 50  | R afferent    |
| 12                          | R, L          | 10    | 43  | ?   | 12   | 40  | 41  | ? L afferent  |
| 13                          | R             | 12    | 33  | 34  | 11   | 33  | 35  | Normal        |
| 14                          | R             | 10    | 43  | 241 | 10   | 243 | 42  | Normal        |
| 15                          | R, L          | —     | —   | —   | —    | —   | —   | R L absent    |
| 16                          | R, L          | 13    | 234 | —   | 13.5 | 39  | —   | ? L afferent  |
| 17                          | R             | 11    | 29  | 235 | 11   | 31  | ?   | ? normal      |
| 18                          | R, L          | 11.5  | ?   | ?   | 11.5 | ?   | ?   | Absent R2     |
| 19                          | R             | 12.5  | 245 | ?   | 11   | 40  | 40  | ? R afferent  |
| 20                          | L             | 11.5  | 31  | 32  | 15   | 40  | 40  | L afferent    |

Blink reflex latencies are given to the nearest 0.5 ms. R2i and R2c indicate ipsilateral R2 and contralateral R2 responses on stimulation of the side stated. ? indicates variable responses and — absent responses. Normal values are taken from Kimura (1975):

|                      | R1   | R2i   | R2c   |
|----------------------|------|-------|-------|
| Mean                 | 10.5 | 31    | 31 ms |
| Range                | 8–13 | 29–41 | 29–44 |
| Interside difference | <1.2 |       |       |

TABLE 4. TRIGEMINAL SENSORY EVOKED POTENTIALS

| Case |                                                                                                                      |
|------|----------------------------------------------------------------------------------------------------------------------|
| 1    | Poorly formed responses with normal latency; absent R V2 response                                                    |
| 2    | Prolonged L V2 latencies (N1 20 ms; P1 30 ms; N2 40 ms)                                                              |
| 3    | Poorly formed responses with probably normal latencies                                                               |
| 6    | Prolonged R V2 latencies (N1 17 ms; P1 26 ms; N2 42 ms; P2 55 ms)                                                    |
| 7    | Poorly formed responses on L; prolonged L V3 latency of N2 (36 ms)                                                   |
| 9    | Normal                                                                                                               |
| 10   | Normal                                                                                                               |
| 11   | Normal                                                                                                               |
| 12   | Normal                                                                                                               |
| 13   | Normal                                                                                                               |
| 14   | Prolonged R V2 latencies (P1 23 ms, interside difference 3 ms)                                                       |
| 15   | Absent response                                                                                                      |
| 17   | Prolonged R V2 and R V3 latencies (P1 24 ms; prolonged P1 and N2 interside differences, 6 ms and 7 ms, respectively) |
| 19   | Normal                                                                                                               |

Abnormal values only are given. Latencies on V2 and V3 stimulation in control subjects (55 measurements) were:

|                      | N1    | P1    | N2    | P2    |
|----------------------|-------|-------|-------|-------|
| Mean                 | 13    | 21    | 30    | 42 ms |
| Range                | 10–15 | 17–23 | 25–36 | 34–54 |
| Interside difference | <3.5  | <2.7  | <5.9  | <12.0 |

dying of ischaemic heart disease contained abundant myelinated fibres (fig. 2). In the patient, electron microscopy (fig. 3) showed many unmyelinated axons and increased endoneurial collagen. Folds of redundant Schwann cell basal lamina were commonly observed (fig. 3). Schwann cells had uniformly pale cytoplasm and often wrapped axons singly but had not initiated remyelination (fig. 4). Perineurial thickness was normal but the perineurial cells were irregularly attenuated and sometimes necrotic, with variable thickening of their basal laminae (fig. 5). Blood vessels appeared normal and inflammatory changes were not seen. The ultrastructural appearance of the autopsy control nerve (figs 6, 7) was similar to that of other peripheral nerves.



FIG. 1. Supraorbital nerve biopsy from Case 15. 1  $\mu$ m section stained with thionin and acridine orange. Bar = 20  $\mu$ m.



FIG. 2. Supraorbital nerve obtained at autopsy from a patient without neurological disease. 1  $\mu$ m section stained with thionin and acridine orange. Bar = 20  $\mu$ m.

## DISCUSSION

The clinical features of our cases of trigeminal neuropathy are similar to those of Cases 1–15 of Spillane and Wells (1959) and of the cases of Teasdall *et al.* (1980). In all cases the dominant clinical feature was trigeminal sensory disturbance. Almost all the patients described the gradual onset of sensory impairment often associated with, or preceded by, positive phenomena such as aching, pricking, dysaesthesia or electric shock-like sensations. Where pain occurred it was not



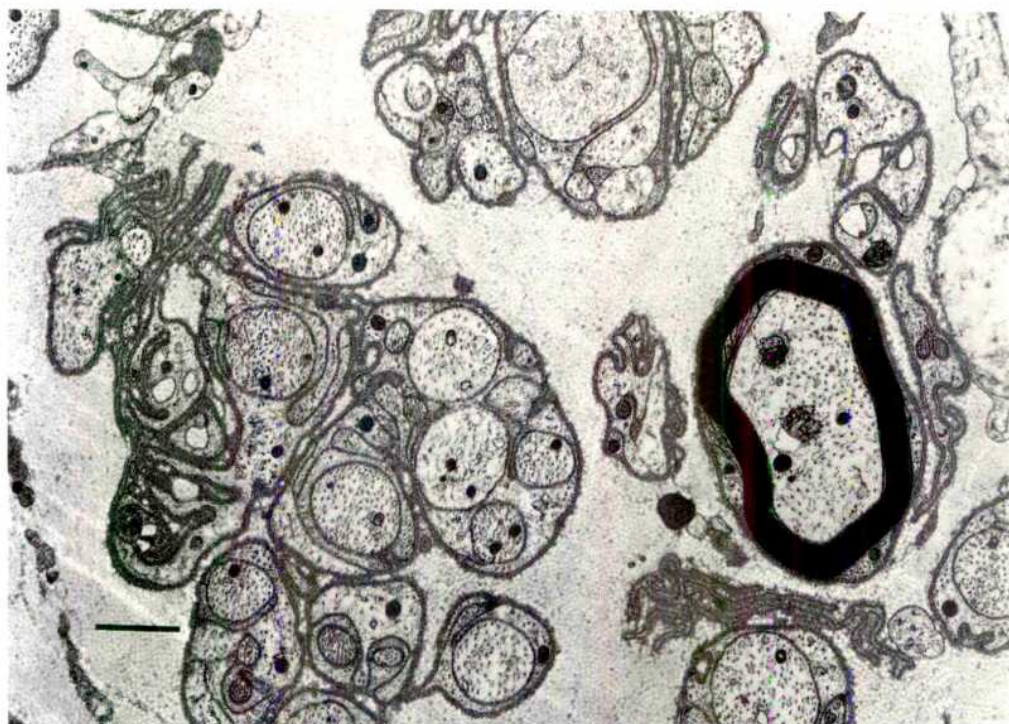


FIG. 3. Electron micrograph of supraorbital nerve from *Case 15*. Note the redundant basal lamina folds, particularly at the top left and bottom right. The myelinated fibre was one of the few remaining. Bar = 1  $\mu$ m.

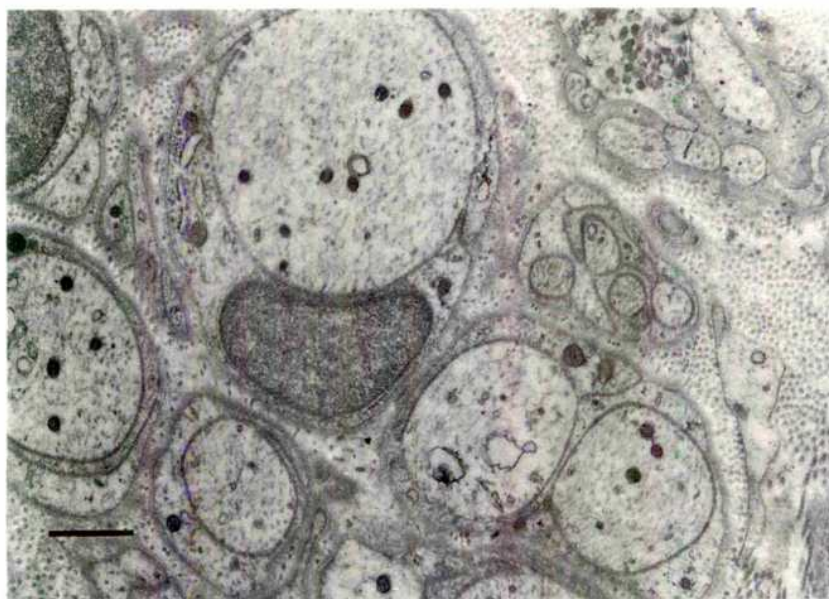


FIG. 4. Electron micrograph of supraorbital nerve from *Case 15*. Bar = 1  $\mu$ m.

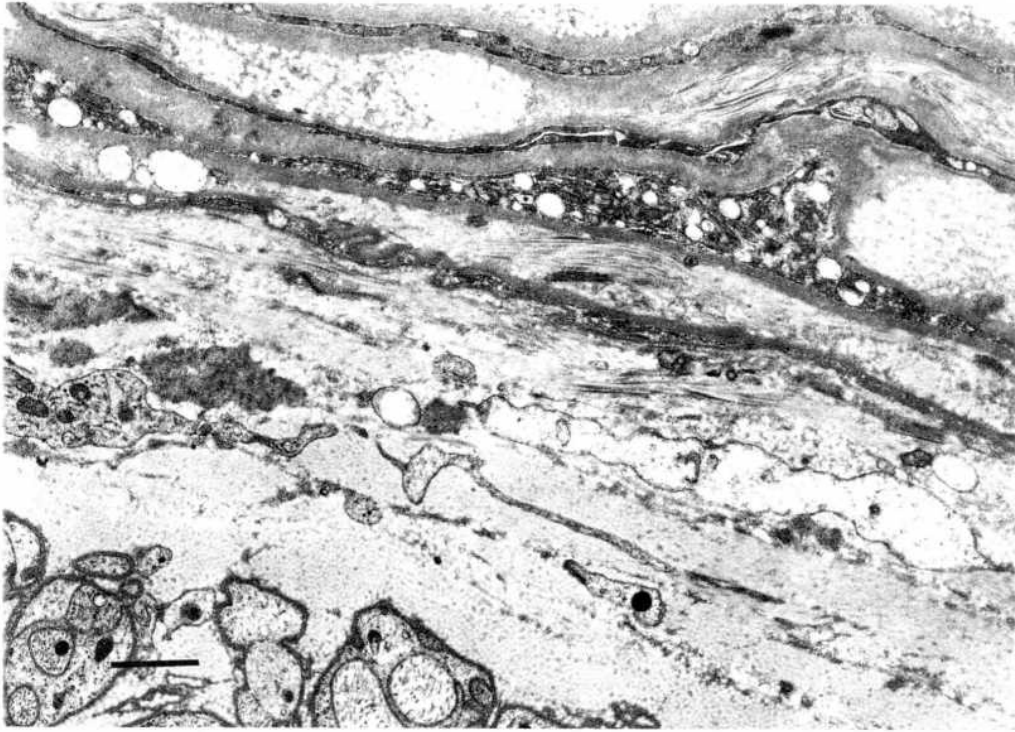


FIG. 5. Electron micrograph of the supraorbital nerve from *Case 15*. The perineurial cells are irregularly attenuated and the basal lamina is irregularly thickened. Bar = 1  $\mu$ m.

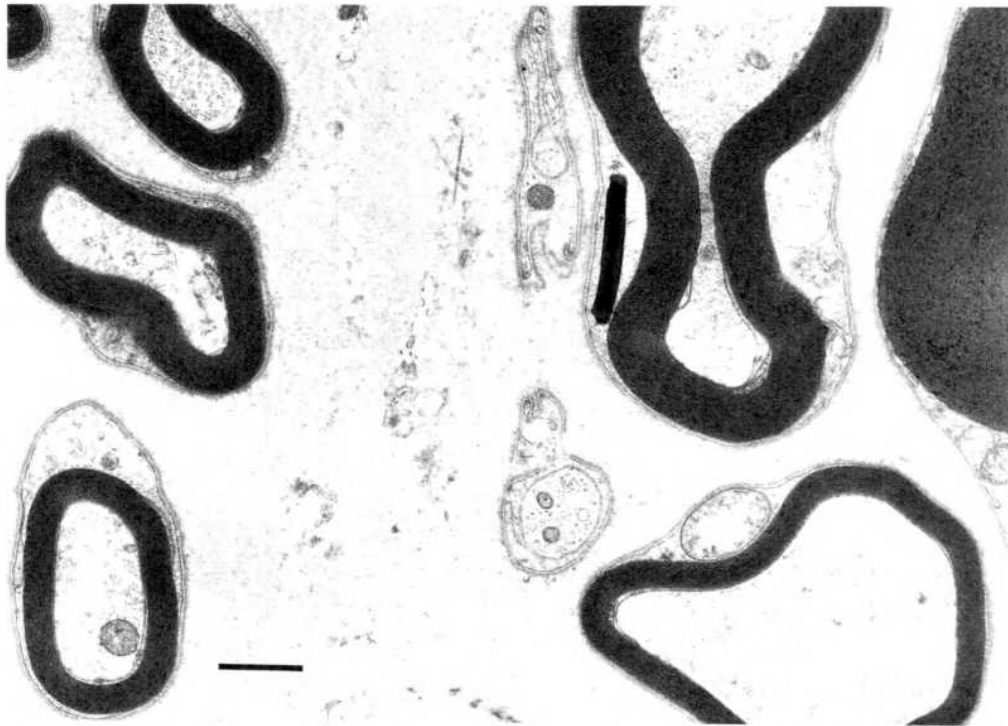


FIG. 6. Electron micrograph of the supraorbital nerve from a patient without neurological disease. There is a normal complement of myelinated nerve fibres exhibiting axonal swelling and mitochondrial changes due to postmortem artefact. Bar = 1  $\mu$ m.



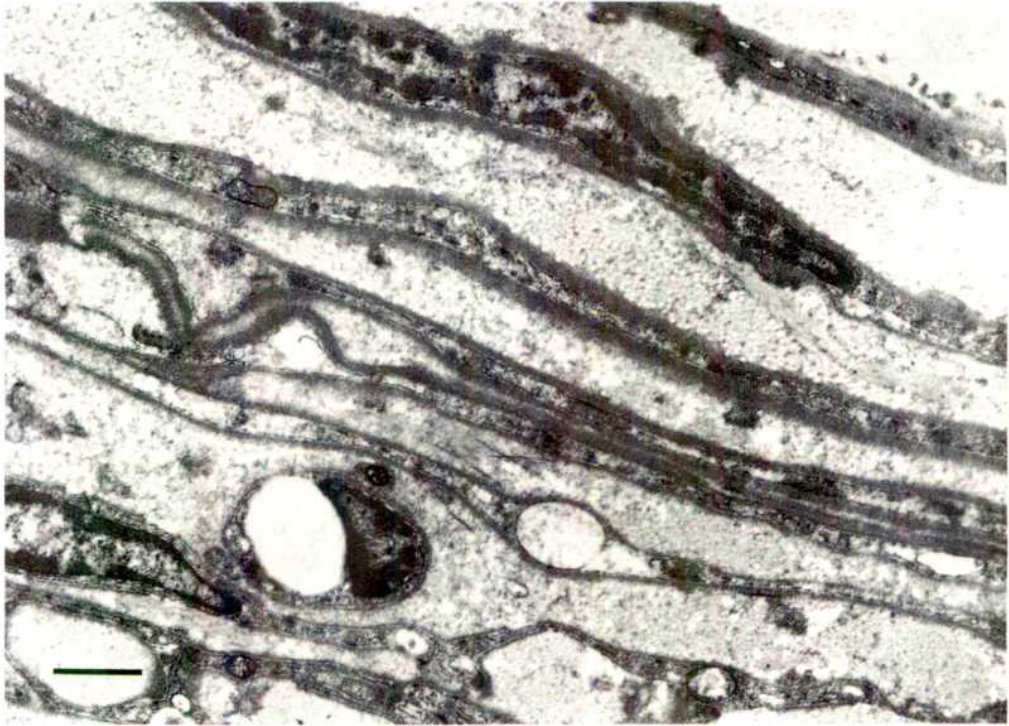


FIG. 7. Electron micrograph from the same nerve as in fig. 6. The perineurial cells have a uniform thickness and may be compared with those in fig. 4. Bar = 1  $\mu$ m.

similar to that of trigeminal neuralgia in that it was usually unprovoked and did not have a paroxysmal or lancinating quality. In 12 cases, the initial disturbance was very localized and, in 11 cases, confined either to the upper or lower lip or to the circumoral region on one side. In Case 11 involvement was initially confined to individual branches of the third division and in Case 9 primary sensation was selectively and severely affected in the territory of both lingual nerves.

Most patients gave a history of gradual extension of sensory impairment over a period of months. In most of the 13 cases with bilateral symptoms or signs, involvement of the second side was sequential and sometimes occurred after a long interval. A higher proportion, 7/9, of the systemic sclerosis/MCTD group had bilateral involvement than the other cases (6/13). Of the 35 affected trigeminal nerve territories, there were signs or definite symptoms in all three divisions in 20. Of the other 15, the first division was involved in 3, the second in 13 and the third in 12. In 14 patients pain, temperature and light touch were affected and in the other 8 light touch was spared. The corneal reflex was depressed or absent in 11 of the 14 cases with first division sensory signs.

Impairment of taste on clinical testing was found in 7/9 of the systemic sclerosis/MCTD group and 8/13 of the others although this was asymptomatic in 3 of

each group. This was also noted by Spillane and Wells (1959) and Teasdall *et al.* (1980), but is not mentioned by Farrell and Medsger (1982).

In the systemic sclerosis/MCTD group (followed for a mean of 8.5 yrs) 6 patients had symptoms and signs which were clearly nonprogressive while 3 reported mild progression. In 7 of the other group (followed for a mean of 4.5 yrs) symptoms had been static for at least 1 yr, 2 were probably slowly progressive and in 4 the duration of symptoms was not long enough to reach a firm conclusion. Only 5 patients reported definite improvement in sensory impairment at some stage although several reported improvement in positive sensory symptoms with the passage of time.

Only Case 11 showed trigeminal motor involvement. Four cases (5, 12, 15, 19) had mild sensorineural deafness. Cases 5 and 12 were elderly and in Case 15 the deafness may have been due to occupational noise exposure. No explanation was found in Case 19 but the neuro-otological findings suggested a cochlear lesion. Several patients complained of difficulty chewing, dysphagia or indistinct speech but this was almost certainly due to sensory loss in the oral cavity rather than motor involvement. No patient had clinical evidence of a more generalized neuropathy.

In 7 patients facial pain was treated with carbamazepine without any definite response. Four patients were also treated with oral corticosteroids without effect on the trigeminal lesion. This is in agreement with Teasdall's observations (Teasdall *et al.*, 1980). Edmondstone *et al.* (1982) reported improvement with steroids in their case, but the period of observation was short.

Among the systemic sclerosis/MCTD group the trigeminal symptoms were the presenting feature and in Cases 1 and 7 led to the diagnosis of an underlying connective tissue disorder. Raynaud's phenomena occurred in all cases in this group and preceded any other symptoms by several years in 5 cases and by more than 20 yrs in 3 of these. In 3 cases no systemic abnormality other than Raynaud's phenomenon was evident at the onset of trigeminal symptoms. The prodromal nature of the trigeminal lesion has been noted by other authors in systemic sclerosis (Beighton *et al.*, 1968; Casey and Lawton, 1971; Teasdall *et al.*, 1980; Farrell and Medsger, 1982; Edmondstone *et al.*, 1982) and in MCTD (Searles *et al.*, 1978).

Raynaud's phenomenon developed in 3 of the other group (Cases 16, 18, 21). In 2 it occurred with the trigeminal symptoms and in 1 it preceded them by 2 yrs. No patient in this group had clinical signs of scleroderma. Indeed none had any clear clinical evidence of an active associated systemic disorder. The only possible exception is Case 18 with a butterfly rash and alopecia. Although this patient showed features suggestive of SLE, current diagnostic criteria for this condition are not met (Tan *et al.*, 1982). One case in this group (Case 10) had a past history typical of rheumatoid arthritis. Case 11 had alopecia areata and Case 12 had pernicious anaemia. In Case 17, with chronic hepatitis, the liver histology was consistent with both chronic active hepatitis and ketoconazole-induced hepatitis. In addition to this apparently high incidence of autoimmune and connective tissue disease, the incidence of some serum antibodies was significantly increased: of the

13 cases, 62% had ANA in titre  $>1:10$  and 23%  $>1:80$  compared with 20% and 3%, respectively, in the neurological controls. Thyroid microsomal 31% (11%) and gastric parietal cell autoantibodies 31% (5%) both occurred more commonly than expected (controls in brackets). The incidence of the other autoantibodies individually did not differ significantly from that found in controls. The incidence in the neurological controls is similar to that noted by Lennon *et al.* (1982) and, as expected, higher than that found in a large adult population survey (Tunbridge *et al.*, 1977). The number of cases in the group is small, but the strength of the association is increased by the number of cases with multiple positive autoantibody titres, excluding ANA; 31% had two or more positive titres while this was found in less than 5% of the controls. Studies such as that of Tunbridge give an incidence of autoantibodies in a wider age range than that of our patients. The incidence of autoantibodies is known to rise with age and, for this reason, we chose to adopt a more rigorous comparison with a neurological control group. The conclusions drawn are, therefore, deliberately cautious.

An association of uncertain significance in Cases 7, 15, 17 and 21 was the reported onset of the symptoms of trigeminal neuropathy after dental sepsis or local anaesthesia for dental extraction or filling. In none of these cases was there any evidence of direct nerve injury. Case 15 also had sinus disease which was a feature in 4 of the 16 cases of Spillane and Wells (1969).

Do the clinical findings localize the site of the lesion? Three prominent features were the initial unilateral circumoral involvement, the high incidence of taste involvement and the absence of motor involvement. Circumoral numbness is occasionally found in transient brainstem ischaemia (Marshall, 1972) and in lesions of the trigeminal spinal tract, the 'onion skin' of Dejerine (1914). However, although a lesion including the nucleus of the solitary tract and the trigeminal spinal tract could explain a coexisting taste and facial sensory disturbance, such a lesion would produce dissociated pain and temperature sensory loss and, especially if bilateral, long tract signs. This was not found, nor was there radiological evidence of brainstem involvement.

Rowbotham (1939) noted impairment or loss of taste in approximately half of 107 published case reports of gasserian ganglion resection. He suggested that taste sensation required a normal background of common sensation. Similarly, Harris (1952) noted that impairment or loss of taste was common after alcohol injection of the gasserian ganglion for trigeminal neuralgia but that persistent impairment was rarer. He refers to 'a common welding of the sensibility of the tongue and palate supplied by the fifth nerve with the true gustatory sensation from the chorda and petrosal nerves'. Although this explanation may apply to the present cases, it seems equally likely that there may be involvement of the taste fibres within the lingual nerves. Lastly, although the classical taste pathway is lingual nerve-chorda tympani-solitary tract, there is evidence in the rat of direct projection of primary trigeminal sensory neurons to the nucleus of the solitary tract (South and Ritter, 1986). Such pathways have not been identified in the human but would provide an



alternative explanation for our observations. Support for the existence of an alternative or accessory taste pathway comes from the report of Grant *et al.* (1987) of abnormal electrogustometric detection thresholds in a variety of trigeminal lesions.

We believe that the sparing of the trigeminal motor pathway, the involvement of individual sensory divisions of the nerve and the lack of dissociation of the sensory loss are all best explained by lesions in the trigeminal ganglion or in the proximal part of the main divisions. The circumoral numbness and taste disturbance is consistent with such a peripheral lesion.

The electrophysiological findings are also consistent with a peripheral lesion but do not aid localization. Kimura (1982, 1983) suggested that the R1 component of the blink reflex is a unilateral pontine reflex arc while the R2 component involves a more complex pathway in the pons and lateral medulla. The expected finding in a sensory trigeminal nerve lesion is an 'afferent' defect, that is, prolongation of the ipsilateral R1 and R2 and contralateral R2 components but with normal R2 latencies on contralateral stimulation. Afferent or probable afferent defects were found in 6 of 17 cases and in another 6 cases latencies were normal. The correlation between corneal reflex findings and blink reflex latencies was not strong. For example, in Case 3 the corneal reflexes were absent but the blink reflex latencies were normal, and in Case 4 the corneal reflexes were normal in the presence of an afferent blink reflex abnormality. A satisfactory explanation for these discrepant findings is difficult but different peripheral pathways are involved as the blink reflex here is elicited by electrical stimulation of the supraorbital nerve rather than corneal tactile stimulation.

The prolongation of the blink reflex latencies was not marked and this is in contrast with the marked prolongation of latencies in demyelinating neuropathies such as the Guillain-Barré syndrome, HMSN type I and chronic inflammatory polyneuropathy (Kimura, 1982). This suggests that the lesions in our subjects were either short: or of axonal type. The TSEP abnormalities noted in some patients correlate reasonably well with the blink reflex abnormalities. With the exception of Case 2, the prolongation of latencies was mild. Again, these findings give no clear evidence as to the localization of the lesion but make a long peripheral demyelinating lesion or a brainstem demyelinating lesion unlikely.

Rushworth (1962) found absent R1 components with normal R2 latencies in 7 patients with partial unilateral first division lesions in whom the blink reflex was elicited by glabella tap. This was found in one of our cases and may not be abnormal (Kimura, 1983). In one of Ashworth and Tait's (1971) cases, the blink reflex was normal, in one probably normal (1 ms asymmetry of R1) and in a third R1 was absent on the affected side. Teasdall *et al.* (1980) found a prolonged facial nerve latency on one side in a patient with bilateral trigeminal neuropathy and absent R1 with symmetric R2 components in another. Several of these patients had normal peripheral motor and sensory nerve conduction studies.

Pathological information about trigeminal sensory neuropathy cases is very scanty. Hughes (1958) described surgical exploration of 3 patients with 'chronic

benign trigeminal paresis'. These differ from our cases in having had a sudden onset although the extent of the numbness then gradually extended. The sensory roots consisted of 'a few wisps of fibres'. Section of the trigeminal ganglion showed cell loss and hyaline change. One of the cases of Spillane and Wells (1959) also underwent exploration of the trigeminal ganglion 2 yrs after the onset of symptoms but with normal findings. They refer to a further case with a 4 month history of facial numbness. Here, the sensory root, the ganglion and the proximal parts of the first and second divisions appeared 'pink and grey' rather than white, the appearances suggesting intrinsic inflammation. The patient subsequently showed subjective and objective improvement. Spillane and Wells and Ashworth and Tait (1971), noting Hughes' surgical observations, favoured a lesion in the ganglion or sensory root.

Teasdall *et al.* (1980), on clinical grounds, argued in favour of a peripheral rather than a proximal lesion, suggesting that a combination of microangiopathy and fibrosis might be responsible. There is no direct evidence as to the nature of the pathological process responsible for the trigeminal lesion. Richter (1954) found thickening of the epineurium and perineurium in the peripheral nerves of a case with peripheral neuropathy and scleroderma. Di Trapani *et al.* (1982) reported that the sural nerve biopsy of a similar case showed complete loss of myelinated fibres, hyperplasia of the Schwann cell basal lamina, and excess collagen in the perineurium and endoneurium. These findings cannot easily be extrapolated to explain the present syndrome because these cases did not have trigeminal symptoms and the trigeminal neuropathy is characteristically *not* associated with generalized neuropathy. Kaltreider and Talal (1969) reported perivascular inflammation and demyelination in the sural nerve of a patient with Sjögren's syndrome and trigeminal neuropathy. The trigeminal nucleus was normal but the nerve itself was not examined pathologically.

Case 15 differs from the others in the severity of the sensory loss. The supraorbital nerve biopsy appearances in this case are correspondingly severe and do not invalidate the conclusions from the electrophysiological studies. The biopsy shows a marked loss of myelinated nerve fibres with survival of unmyelinated fibres. The damage must have occurred at or distal to the trigeminal sensory ganglion, but the cause is necessarily speculative. Vasculitis affecting the trigeminal nerve branches, particularly where they are tightly invested by dura and more susceptible to oedema and consequent rise in endoneurial pressure, seems possible in the context of autoimmune diseases. Alternatively fibrosis of the epineurium and perineurium proximally might increase the endoneurial pressure and preferentially damage myelinated fibres. The degenerative changes in the perineurium shown in Case 15 are nonspecific in type.

The question why the trigeminal sensory fibres should be selectively involved remains unanswered. There is experimental evidence that the blood vessels of the trigeminal ganglion are much more permeable to proteins than the blood-brain barrier. In the rat, horseradish peroxidase passes from venous blood into the

extracellular space of the trigeminal ganglion within 2 min to penetrate the endoneurial space within 5 min (Jacobs *et al.*, 1976). It could be speculated that the selective trigeminal lesions result from the entry into the ganglion of some neurotoxic serum factor.

These cases show that the clinical features of trigeminal sensory neuropathy occurring in association with systemic sclerosis or MCTD are indistinguishable from cases occurring in isolation. Amongst the latter 'idiopathic' group, the high incidence of associated autoimmune disorders and serum autoantibodies, especially ANA, suggests an association with disturbed autoimmunity. The aetiology in this group may well be heterogeneous. It is clear both from other reports and the present series that trigeminal sensory neuropathy may be the harbinger of systemic sclerosis or MCTD. Elucidation of the mechanisms will require further pathological studies, particularly on autopsy material.

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## DISTURBANCES IN CONCEPTUAL SPACE INVOLVING LANGUAGE AND SPEECH

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### SUMMARY

We report on a patient, with a CT-verified low density lesion in the right parietal area, who exhibited not only deficits in left conceptual space, but also in reading, writing, and the production of speech. He presented with a left homonymous hemianopia, tactile inattention, and dysphasia that quickly resolved, leaving a left-sided inattention and less marked dysphasia. Several language tasks and language-based imagery tasks revealed poor language processing of the left portion of words which could be remedied if the patient was instructed to do things like spell the word backwards. The overall results were consistent with the idea that some aspects of language processing involve spatial mechanisms.

### INTRODUCTION

Unilateral neglect has traditionally and commonly referred to the failure to respond to information from the hemispace contralateral to a parietal lobe lesion, although other lesions can also produce the phenomenon. Such patients also fail to incorporate into actions information that normally falls into the neglected field. Thus patients with right hemisphere disease affecting visual processes ignore the left side of a printed page while attempting to read. When trying to draw they typically draw only one half of an object, such as a clock, but nonetheless claim to have drawn it completely. Although the neglect phenomenon most frequently involves visual processes, it is also seen with tactile and auditory stimuli.

The classical picture of neglect phenomena has undergone several interesting modifications. Kinsbourne and Warrington (1962) reported 6 cases with right parietal disease who failed to read the left side of words, no matter where they appeared in their visual field. This was true even when the words were presented tachistoscopically all within the intact right visual field. These results were consistent with the view that neglect involved the left half of information no matter where it appeared, and for the first time suggested that the dysfunction involved a deficit in left conceptual space as opposed to left retinotopic space. This idea was

confirmed and extended by Bisiach and Luzzatti (1978) who reported 2 cases with left hemispatial neglect who failed to report the shops on the left half of the Piazza del Duomo in Milan when imagining that they were standing in front of the Cathedral looking across the Piazza. Conversely, when imagining they were across the Piazza looking at the front of the Cathedral, they were able to report the shops ignored in the first condition but now failed to mention the shops previously described. This ingenious study further supported the idea that the parietal lobe was active in organizing information in conceptual space.

In the present study we report a patient who demonstrated not only deficits in conceptual space of the type already described, but also deficits in the production of speech and in writing that relate in a systematic way to a left hemispatial neglect. This case is remarkably similar to one reported by Baxter and Warrington (1983). In the early phases of testing, the overall picture was clouded by a confounding dysphasia as the patient was left handed. This condition largely cleared, however, and the pattern of the patient's mistakes was found to be more consistent with a deficit in spatial abilities. In short, through careful examination, we were able to determine crucial dissociations of function at a cognitive level of activity.

### CASE REPORT

J. L. is a 71-year-old retired lawyer, admitted to New York Hospital a few hours after the acute onset of speech difficulty. He was left handed for most activities except writing, having been forced to use his right hand as a child. There was a family history of sinistrality.

At 1.00 a.m. on the day of admission, he noticed he was talking gibberish. On trying to read, he reported seeing only the right side of a printed page and was equally incomprehensible when trying to read aloud to his son. He was aware of his abnormality.

He was first examined 8 h later. He had a left homonymous hemianopia and tactile inattention. He was clearly dysphasic. The dysphasia was fluent with moderate anomia, literal paraphasic errors and difficulty with repetition. He was also markedly dysgraphic and alexic. He bisected a line to the right of the midline and described only the right side of a picture. CT scan of the brain showed a low density lesion in the right parietal area.

Within 24 h after onset, the visual field defect had resolved, leaving left-sided extinction under conditions of double simultaneous stimulation. At this time, visual evoked potentials were performed. Thus at a time when the patient clearly showed extinction of information in the left visual field, the latencies of visual evoked (P100) potentials were symmetric and normal. The dysphasia was much less marked, with few paraphasic errors. Some reading and writing was now possible. On the second day, the Boston Diagnostic Aphasia Examination was administered, confirming the general clinical picture.

### OBSERVATIONS

Throughout all tests, there was an evolving course evident for most of the phenomena reported. In what follows we describe this course for each set of observations. We begin by reporting the capacity of the patient to process written information presented in free view and with no time constraints on his rate of reporting. Next, we report on the patient's executive skills with detailed descriptions

of his ability to speak, spell and write. Finally, we report on an American attempt to reproduce the Piazza effect and show an inability to access internally-represented visual information in the left visual hemisphere.

### *Reading*

On day 1, the patient was admitted, but not seen or examined by us. On day 2, he was alexic, although he could decipher individual letters. On day 3, he was asked to read 68 words presented individually. The words varied in length and frequency of use. He could manage 2 and 3-letter words with little difficulty; however, he made a total of 16 errors (23%) on words longer than 3 letters. Mistakes occurred mostly at the beginning of words (*see Table*), consisting of omissions and sub-

TABLE. READING ERRORS ON DAY 3

| <i>Stimulus</i> | <i>Response</i> | <i>Stimulus</i> | <i>Response</i> |
|-----------------|-----------------|-----------------|-----------------|
| 1. Nasty        | Masty           | 9. Bequeath     | Queath          |
| 2. Hastily      | Gastily         | 10. Surround    | Sround          |
| 3. Very         | Neverly         | 11. Tractor     | Doctor          |
| 4. Rattle       | Mattle          | 12. Importance  | Portance        |
| 5. Variety      | Charity         | 13. Fled        | Sped            |
| 6. Astonish     | Tonish          | 14. Heath       | Eath            |
| 7. Flamboyant   | Ambouyant       | 15. Dining      | Nining          |
| 8. Deserve      | Observe         | 16. Know        | Now             |

stitutions, in the latter instance sometimes forming other real words. On the fourth day only 10 words, 9–12 letters in length, were tested individually and errors were made on half of them. On days 5 to 7, the test consisted of reading a text that varied each day. By this time the error rate had dropped considerably: day 5, 7/291; day 6, 21/308; day 7, 9/167. Still, all errors occurred in words of longer than 3 letters, and occurred in the leftmost letters.

### *Oral spelling*

Spelling was tested on day 3. In this test the subject was read a word aloud such as 'cat'. The task was to spell out each of 15 spoken words (10 three letter and 5 four letter). The words were presented one at a time and response was made after each spoken word. The results are plotted in fig. 1. The graded increase in error rates towards the beginning of words, and the added effect of increasing word length can be seen. As with writing, mistakes consisted of omissions or substitutions.

### *Spontaneous speech*

Consistent with the foregoing picture of a failure to process the most leftward letters in a word in both reading and spelling tests, some limited observations were made on spontaneous speech. It was brought to our attention by the patient's son that his father seemed to be omitting the beginning of words. He had said '—balance' instead of 'ambulance' and '—portant' instead of 'important'. Over the



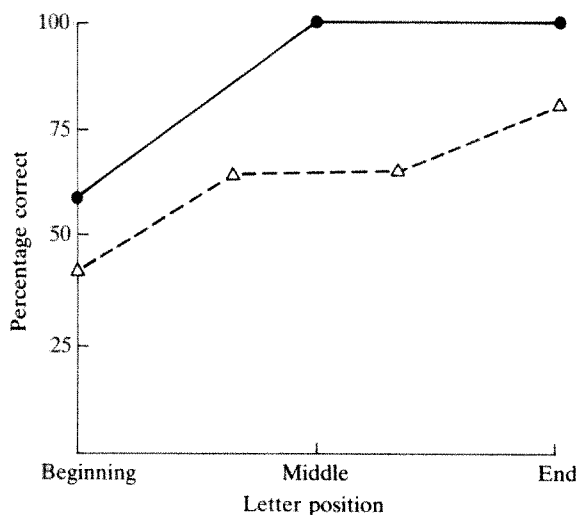


FIG. 1. Percentage error frequency in oral spelling of words. More errors were made at the beginning of 3 and 4-letter words. Solid circles and line = 3-letter words. Triangles and broken line = 4-letter words.

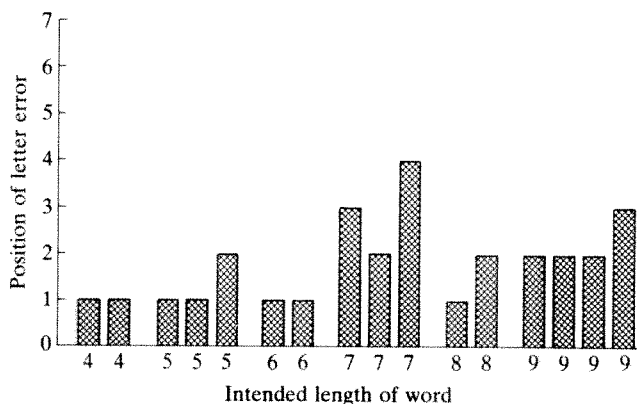


FIG. 2. Position of letter error in relation to intended word length during spontaneous speech. Over a 10-day period several examples were noted where the patient omitted the beginnings of letters for words of a variety of lengths.

next ten days we observed 16 such mistakes, mostly of omission, but also substitutions often forming semantically unrelated words (fig. 2).

### *Writing tests*

At the time of testing for writing ability on day 2, the patient could reproduce the alphabet without any errors. However, on attempting to write words to dictation (26 words), he would start at the end of a word and work backwards, managing only the last few letters without any mistakes and often leaving out the beginnings of words. He was perfectly aware of the deficit in all cases and was able to tell how many letters were missing (or wrong) at the beginning of words. On attempting to

write 'come', for example, he wrote 'ome' and said 'I know there is one letter over here but I can't get it'.

On the third day after admission, he was tested on a total of 13 words. He managed most 3-letter words, although still backwards. As in the case of 'dog', it frequently took several attempts to produce all the letters correctly, working one letter at a time from the end backwards. His span improved daily, proceeding in a right to left direction so that by the end of the first week, he could manage words of virtually any length, although errors remained higher at the beginning of words. Fig. 3 shows the percentage correct for each letter position on days 2 to 4. On day

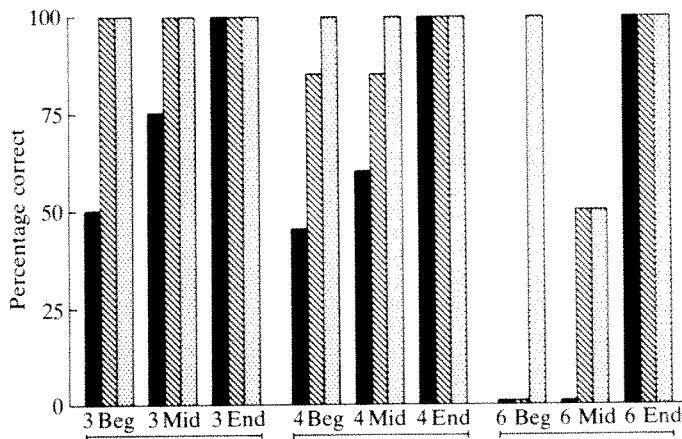


FIG. 3. Response of patient to writing to dictation 3, 4 and 6-letter words showing position in word where most errors were made. Improvement is seen with time. Solid area = day 2; cross-hatched area = day 3; speckled area = day 4.

4 only a few words were tested as he was clearly no longer impaired on the test. The gradation of error rates and the effect of word length is demonstrated, with higher error rates at the beginning of longer words. Error rate increased with distance from the last letter.

For the word 'blue', as the patient had written 'b-ue' and could not 'see' the 1, he was asked to write it in reverse, starting with B on the right. As seen in fig. 4,

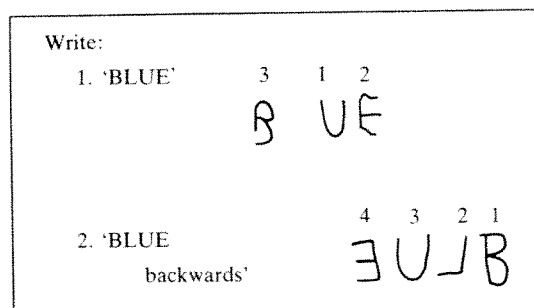


FIG. 4. Examples of writing to command. There was a tendency to omit the first letter of a word or to write it last. If asked to write the word backwards, the first letter was written first.

the missing letter became 'visible' and the whole word was written without hesitation. Two other examples were tried in this manner and, interestingly, the mistakes were again made at the beginning of the word, on the right side of the paper. This result was consistent with the view that writing involved imaging processes that were affected by his disorder such that the left half of imaginal space was not functioning normally. This idea prompted the final observation described below.

### *Spatial representation*

An effort was made to determine whether or not the patient would show difficulties in accessing information falling into an internal conceptual hemispace. A test of general imagery was given which required the patient to describe from memory the spatial location of certain elements when viewed from a particular vantage point. The test was given on day 3 and again before his discharge from hospital. In this test the patient was asked to imagine that he was standing in New York with his back to the ocean, facing California, and to name the states which lay in between. The results are shown in fig. 5. On day 3, 10 states were named, all

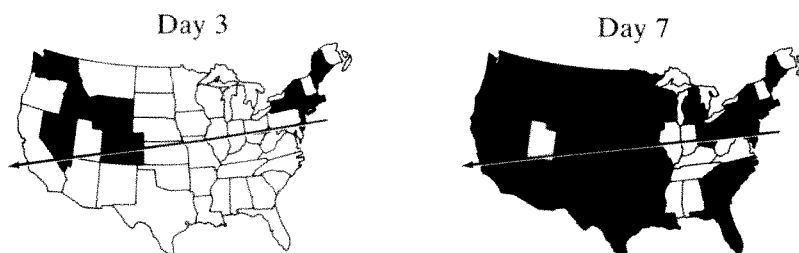


FIG. 5. The patient was tested on his capacity to recall American states when he adopted a vantage point looking west from the George Washington Bridge in New York City to California. His initial report, occurring during the period of severe inattention, showed a failure to recall states falling into left conceptual space. Some days later he reported almost all states.

to the right of the line representing the imaginary direction of gaze. Unfortunately the patient then became tired and it was not possible to run the converse test using an eastwardly looking vantage point. Before discharge, however, and with the same original instructions, he managed to name most states, leaving out 6 to the left of the line and 3 to the right. At this time, he was making only occasional paralexia mistakes and there was no tactile inattention.

### DISCUSSION

The foregoing observations appear to support the general view that right-sided parietal lesions can cause disturbances in left conceptual space. Consistent with earlier observations (Kinsbourne and Warrington, 1962; Bisiach and Luzatti, 1978), the patient produced results suggesting that visual information falling into the left part of a conceptual space was inaccessible to conscious report. In addition, the

present observations suggest that this deficiency in accessing information in left conceptual space can extend into the executive functions of language including oral spelling and spontaneous speech. The case as described is remarkably similar to the patient reported by Baxter and Warrington (1983). Both were left handed and experienced insults to their right parietal cortex. Both were dysphasic at onset. Their observations were also made acutely as well as after a nine-month interval. Their patient also showed the letter effect on spelling and this persisted when attempting to spell backwards. Interestingly, their patient also tended to write the last letters first when trying to spell forwards. In the following we argue this constellation of deficits, which impairs both perceptual and language processes in left conceptual space, reflects damage to two separate spatial systems, a disturbance that becomes uniquely observable in damage to left handers with right hemisphere dominance.

It has recently been determined that in right handers, language-related processing may be relatively impervious to the influence of neglect due to right hemisphere damage. This is evidenced by the finding of Tzeng and Hung (1987) that in Chinese, there is a left neglect of pseudoideograms but not of genuine Chinese characters in spite of the similar visuospatial attributes of the two figure types. M. Sieroff and M.I. Posner (personal communication, 1986) have found a similar lack of vulnerability in words relative to nonwords in English speaking subjects with left neglect. In a related observation, it has been shown that deaf patients with right parietal lesions who communicate with American Sign Language are impaired in their left conceptual space for perceptual space but not for language expression (Bellugi and Klima, 1987). Taken together, these studies have been interpreted as suggesting that some kind of 'top-down' process in the language system can override the attentional deficits produced by the right parietal lesion.

Alternatively, and more consistent with the present findings, is the view that there are spatial processes specifically associated with language use which are typically spared in neglect patients. These processes, which are most probably associated with language systems in the left hemisphere, are spared with right parietal lesions when the language system is in the left hemisphere. In the present left-handed case and in the patient of Baxter and Warrington, the right hemisphere is doing double duty by necessarily managing both language and perceptual processes. Damage to these patients creates disturbances in both spatial systems.

Further support for this view comes from observations on split-brain patients. These patients have never revealed the type of errors seen here. In the split-brain patient the left hemisphere is cortically disconnected from the right hemisphere. This might lead to the proposal that the left hemisphere should behave as if it processed information without the advantages of the right parietal systems and the right without the advantages of the left parietal system. However, when it comes to writing, spelling, and speaking from the left hemisphere, deficits of this type are not seen. This would be predicted if special spatial systems associated with language processes were managed by the left hemisphere. Additionally, the disconnection

model does hold for some aspects of spatial attention. In a series of studies examining how hemisphere disconnection affects gravitational coordinates in attentional processes, it has been demonstrated that the left disconnected hemisphere behaves as if the right hemisphere were lesioned and in the same patient the right hemisphere behaves as if the left hemisphere were lesioned (Gazzaniga and Ladavas, 1986). Taken together, this suggests that the attentional systems active in the imaging processes of a hemiconceptual space are distinct from those associated with directing attention to points in physical space.

It is also of interest to consider these deficits in conceptual space in light of more traditional studies on mental imagery. The experimental investigation of imaging systems has been extensive in recent years and several ideas have emerged as to how mental imagery is accomplished. Some have argued imaging systems have an identity with perceptual systems and that they share the same brain processes (Shepard, 1982). Others have maintained that imagery is the product of propositional features of language systems and is not a distinct aspect of the cognitive system (Pylyshyn, 1981). Yet the dominant view is that mental imagery is a distinct mental system and that mental images are generated by the interaction of several identifiable component processes such as image generation, image rotation, and image scanning, to mention but a few (*see Kosslyn et al., 1979*).

The present results, as well as others, raise problems for the perceptual hypothesis. Patients who have difficulty accessing imaged information are not impaired in simple measures that examine the integrity of the perceptual systems. For stored information, if they change their vantage point for inspecting an image, once-neglected information is accessed. Other studies have shown that information that falls into an extinguished field is processed in a perceptual task, albeit outside the realm of consciousness (Volpe *et al.*, 1979). Finally, patients who have undergone partial commissurotomy that interrupts interhemispheric transfer of tactile but not visual information, reveal a pattern of results on imagery tests that suggest imagery systems are not connected to visual cortical processes (Gazzaniga, 1985). In these studies, patients presented with an object in, say, the right hand, could not find its match with the left hand. However, if a picture of the object was presented to either hemifield, they could find the matching stimulus with the left hand. This shows that when the object appeared in the right visual field, the remaining intact callosal fibres transmitted information about the visual stimulus over to the right hemisphere for use by the somatosensory system. These same patients, however, failed to use these intact visual fibres when the instructions to the patient were to make 'an image' of the object placed in their right hand before trying to find the match with their left. While the patients claimed to have made an image and while tests of their overall capacity to make images were positive, this strategy did not promote integration of information over their remaining and clearly functional neuronal pathways.

The view that imagined processes are epiphenomenal to propositional language is also not supported by the present results as well as other studies. The propositional

language system is wholly intact in such cases, where clear deficits exist in imaged space. Additionally, results of imagery studies on split-brain patients are not consistent with this view (Farah *et al.*, 1985; Kosslyn *et al.*, 1985). The most extensively studied patient examined in these studies, Case J. W., possessed propositional language in only the left hemisphere. The right hemisphere possessed a rich lexical system but little or no syntax or the capacity to make simple inferences. Results to date on this patient suggest that some features of the imaging process are normally carried out in the left hemisphere, such as the ability to assess details of a globally generated image. At the same time, both hemispheres seem capable of generating images of the type needed to draw objects and localize points in imaged space (personal unpublished observations). Taken together, it would appear that each half brain can have imaging processes related to perceptual processes.

#### ACKNOWLEDGEMENTS

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# AN ELECTROPHYSIOLOGICAL INVESTIGATION INTO THE PAIN-RELIEVING EFFECTS OF HETEROTOPIC NOCICEPTIVE STIMULI

## PROBABLE INVOLVEMENT OF A SUPRASPINAL LOOP

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### SUMMARY

It has previously been shown that, in normal subjects, heterotopic painful stimuli induce parallel decreases in the sensation of pain and the nociceptive spinal flexion reflex RIII simultaneously evoked by electrical stimulation of the sural nerve. By contrast, heterotopic nonnoxious stimuli were ineffective in this respect. In order to assess the possible involvement of supraspinal structures in these changes, we have now compared the effects of nociceptive electrical stimuli applied to the fourth and fifth fingers of the hand on the contralateral RIII reflex in 5 normal subjects and 5 tetraplegic patients suffering from a clinically complete spinal cord transection of traumatic origin. The tetraplegic patient had a C5, C6 or C7 spinal cord transection with lower segments, notably C8 and T1, clinically uninjured. In these patients, sural nerve stimulation induced a biceps femoris reflex which did not differ from the RIII reflex recorded in normal subjects, either in terms of latency or of threshold.

In both groups, the RIII reflex threshold was determined and a juxtathreshold RIII reflex was studied before, during and after a 2 min period of conditioning stimulation. The conditioning procedure consisted of nociceptive electrical stimulation applied to the digital branches of the ulnar nerve which arises from C8 and T1, i.e., below the level of the patients' spinal transection. In normal subjects such conditioning elicited painful sensations of 'pin prick', 'burning' and 'squeezing'. It simultaneously induced a strong inhibition of the RIII reflex which outlasted the conditioning period by several minutes. By contrast, nonnociceptive electrical conditioning stimuli (0.1 ms duration pulses of 6 to 8 mA intensity, at 3/s), similarly applied to the digital branches of the ulnar nerve were totally ineffective. In tetraplegic patients not only was the RIII reflex never decreased by the heterotopic nociceptive stimulation but it was, in fact, slightly enhanced.

These results show that the effects of heterotopic nociceptive stimulation observed in normal man are possibly mediated by a complex loop involving supraspinal structures. This further underlines the similarity between this phenomenon and the Diffuse Noxious Inhibitory Controls (DNIC)



described in the rat, since the latter are observed in intact but not in spinal animals. These findings are discussed with reference to counterirritation phenomena and procedures aimed at producing analgesia by somatic electrical stimulation.

## INTRODUCTION

We previously reported that in normal human subjects, heterotopic painful stimulation depressed both the nociceptive spinal reflex RIII and the corresponding pain sensation triggered by sural nerve stimulation; heterotopic nonnociceptive stimuli were ineffective in this respect (Willer *et al.*, 1984). These results suggested that the modulation of pain by heterotopic nociceptive stimuli could be explained, at least in part, by a spinal depression of the transmission of nociceptive signals. This type of effect could represent the neural basis for counter-irritation phenomena, that is, the paradoxical pain relief produced by painful stimulation of heterotopic areas of the body (for references, see Le Bars *et al.*, 1984). It was suggested, on the basis of analogous animal studies, that such phenomena might be sustained by a complex loop ascending from and descending to the spinal cord. The aim of the present work was to test this hypothesis by comparing the effects of a heterotopic stimulus on the RIII reflex in normal subjects with those observed in tetraplegic patients suffering from a clinically complete spinal cord transection of traumatic origin. Since the natural stimuli previously used could be harmful to these patients, we decided to employ electrical conditioning stimuli.

## METHODS

### *Subjects*

Ten subjects volunteered for this study: 5 normal subjects and 5 patients suffering from a complete cervical spinal cord transection. All gave their consent after being informed of the experimental aim of the study, according to the principles of the Helsinki convention. The normal subjects (4 males, 1 female, 24–45 yrs old) were members of the laboratory staff familiar with the experimental procedure.

The patients were male inpatients from a rehabilitation centre and all suffered from tetraplegia due to a traumatic section of the C5, C6 or C7 spinal cord; since the patients were unable to perform any voluntary movement and had total sensory loss below C7 or T3 (1 subject), the transections were judged to be clinically complete. The time interval from the injury (3–13 months) had allowed the recovery of spinal reflexes (see Table 1). In all the patients, the C8 and T1 segments were considered to be uninjured since (1) the flexor digitorum tendon jerk reflex was present; (2) muscular responses of intrinsic hand muscles were obtained following electrical stimulation of the ulnar nerve trunk; (3) Horner's syndrome was not observed, thus indicating that the T1 segment was undamaged.

At the time of the experimental session, the patients were free from pressure sores, urinary tract infection or other medical complications. Patients with severe autonomic dysfunction were not included in the study. During the sessions, the normal subjects sat comfortably and reclined in an armchair. The tetraplegic patients lay on a bed.

### *Test procedure*

The method for eliciting and recording the nociceptive flexion reflex (RIII) has been fully described elsewhere (Willer *et al.*, 1984). Briefly, bipolar electrical test stimuli were applied to the sural nerve via a pair of surface electrodes (20 mm apart) placed over its submalleolar path. The stimulus

TABLE 1. PRINCIPAL CLINICAL DETAILS CONCERNING THE SPINAL LESIONS OF THE TETRAPLEGIC PATIENTS

|                                          |    |    |    |    |    |
|------------------------------------------|----|----|----|----|----|
| Age (yrs)                                | 22 | 19 | 35 | 32 | 17 |
| Time elapsed from injury (months)        | 13 | 3  | 9  | 11 | 9  |
| Level of total motor loss                | C6 | C6 | C6 | C7 | C5 |
| Level of total sensory loss              | C7 | T3 | C7 | C7 | C7 |
| Tendon jerk C6 (biceps, brachioradialis) | ++ | +  | -  | +  | +  |
| Tendon jerk C7 (triceps)                 | ++ | -  | ++ | -  | +  |
| Tendon jerk C8-T1 (flexor digitorum)     | ++ | ++ | ++ | ++ | +  |
| Flexor spasms in lower limbs             | ++ | ++ | ++ | ++ | ++ |

- = none; + = present; ++ = brisk.

consisted of a 20 ms duration volley of 8 rectangular pulses (1 ms duration) and was delivered once every 6 s from a constant current stimulator. Electromyographic (EMG) responses were recorded from the ipsilateral biceps femoris muscle, via a pair of surface electrodes fixed on the degreased skin overlying the muscle. The intensity of stimulation was adjusted to 20% above the RIII reflex threshold, which gave rise to stable responses with minimal fluctuations. Such a stimulus induced a slightly painful pin prick type sensation in normal subjects. Both the reflex responses and the stimulation intensities, by means of a current probe, were continuously monitored on a storage oscilloscope during the experiment.

#### *Conditioning procedures*

The nociceptive conditioning procedure consisted of electrical stimulation (1 ms duration pulses at 3/s) applied by means of two ring electrodes tied around the fourth and fifth fingers of the contralateral hand. In normal subjects the intensity was adjusted to the maximum they could tolerate (25–30 mA). Identical intensities of stimulation were used in the tetraplegic patients. To verify further the lack of effect of heterotopic nonnoxious stimuli in normal subjects, a nonnociceptive procedure was used with the parameters of electrical conditioning stimulation being adjusted to give rise to a tactile sensation: 0.1 ms duration, 6 to 8 mA at 3/s. The test and conditioning stimuli were delivered in such a fashion that the RIII reflex was not invaded by any stimulus artefact.

The EMG responses were digitized at 100 Hz by an on-line computerized system. Each response was full-wave rectified and integrated between set points on the waveform which were chosen for each subject in accordance with the latency and duration of the RIII reflex, usually from 100 to 180 ms following the stimulus onset (see examples in fig. 1).

#### *Experimental procedure*

At the beginning of a session, both the test and the conditioning stimulus intensities were adjusted as described above. Then the test stimuli were applied for at least 12 min with the conditioning stimuli being delivered during the sixth and seventh minutes.

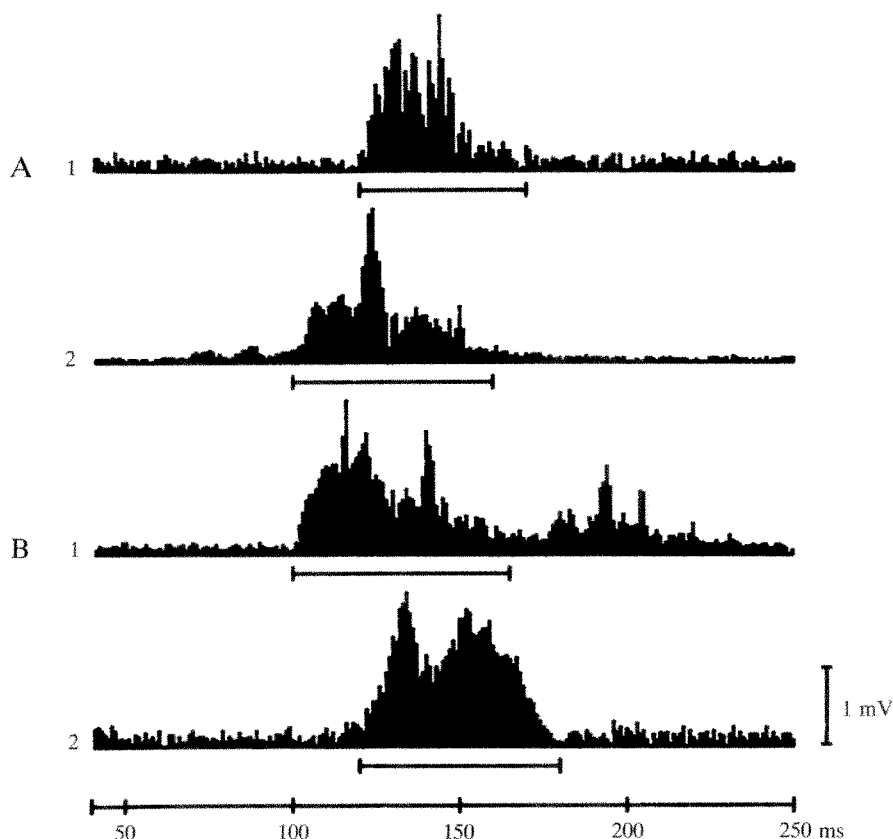


Fig. 1. Individual example of full-wave rectified averaged (10 presentations) RIII reflexes in normal (A) and tetraplegic (B) subjects. The time window used for quantifying the RIII activity was adjusted for each subject as indicated by the horizontal bar below each response.

#### *Analysis of results*

For each subject, control responses were determined during the 2 min preceding the conditioning period. The mean control value was then calculated and each individual reflex response was expressed as a percentage of this mean. The means of 10 successive responses were calculated for each minute of the procedure. Statistical analyses (Student's *t* test) were performed using these mean values.

## RESULTS

### *Characteristics of control responses in normal subjects and tetraplegic patients (fig. 1)*

In the 5 normal subjects the mean threshold for obtaining a nociceptive flexion reflex (RIII) was  $9.2 \pm 2.6$  mA. Increasing the current to a slightly suprathreshold intensity (+ 20%) gave rise to a supraliminal RIII reflex (mean latency  $112 \pm 9$  ms). As previously described (Willer, 1985), the reflex did not exhibit any noticeable change during the repeated application of the stimulus.

In the 5 tetraplegic patients, a response with a similar latency (mean  $119 \pm 7.4$  ms) was observed. The mean threshold for this response ( $9.8 \pm 4.9$  mA) was very similar to the RIII reflex threshold in normal subjects. As in normal subjects, the responses remained nearly constant during the reapplication of the stimulus. In 4 patients, the RIII reflex, which typically lasted less than 100 ms, was followed by a later response (*see* fig. 1B1). These later responses were also observed with lower intensities of stimulation (i.e., 3–4 mA), indicating that they were not involved in nociceptive processes (Roby-Brami and Bussel, 1987) and were not considered for further analysis.

#### *Effects of heterotopic conditioning stimulation in normal subjects*

The 3 Hz nociceptive electrical stimulation of the fingers induced rhythmic painful sensations described as being like pin prick with additional burning and squeezing sensations reported as originating from deep structures. As illustrated with a representative individual example in fig. 2, the conditioning stimuli induced a strong inhibition of the RIII reflex. This inhibition occurred rapidly within the first minute, lasted throughout the conditioning period and only gradually recovered during the following 5 min. Similar effects were observed for all 5 subjects with the RIII reflex being totally suppressed in 3 of them during the nociceptive heterotopic stimulation. In 1 subject, the conditioning induced a slow onset

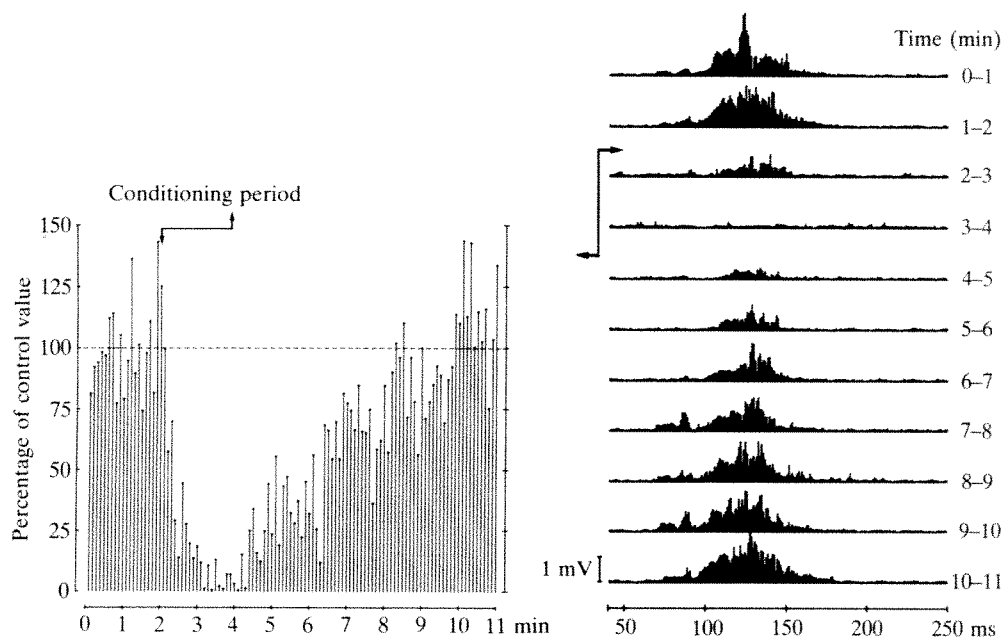


Fig. 2. Individual example of the effects of heterotopic nociceptive stimulation upon the RIII reflex in a normal subject. *Left*, each bar represents a single reflex response expressed as a percentage of control (0–2 min) values. *Right*, each trace represents the average of 10 responses recorded within 1 min. In both instances, the conditioning period is indicated by arrows.

depression of the reflex while in another, the inhibitory poststimulus effects lasted for as long as 8 min following the end of the conditioning period. By contrast, the 3 Hz nonnociceptive electrical stimulation of the fingers induced a rhythmic tactile sensation, and in all the subjects, this type of conditioning stimulation produced no significant change in the RII reflex.

The overall effects are summarized in fig. 3.

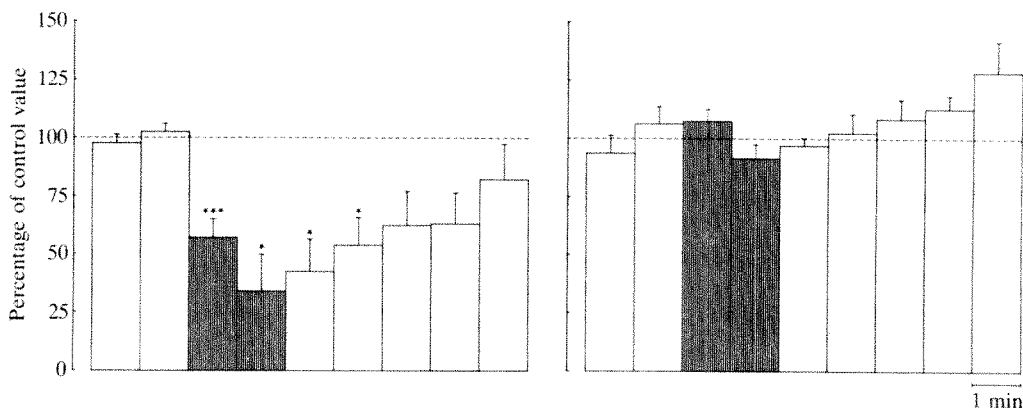


Fig. 3. Mean results obtained with normal subjects before, during (hatched area) and after the nociceptive (*left*) and nonnociceptive (*right*) conditioning period. Data are expressed as percentages of control values recorded during the 2 min control period, \*  $P < 0.02$ , \*\*\*  $P < 0.001$ .

#### *Effects of nociceptive heterotopic conditioning stimulation in tetraplegic patients*

As illustrated with a representative example in fig. 4, the conditioning stimulation did not produce any depression of the RII reflex. Similar results were observed in all 5 patients and the grand average illustrated in fig. 5 shows, on the contrary, a significant enhancement of the responses although this effect was variable and was significant only during the first minute of conditioning and the first minute after the conditioning period.

### DISCUSSION

The present results demonstrate that nociceptive electrical conditioning stimuli applied to an anatomically remote area of the body (the fourth and fifth fingers of the right hand), in normal subjects, produced a profound depression, followed by long-lasting after-effects, of the left nociceptive flexion reflex elicited by sural nerve stimulation. By contrast, the same conditioning procedure did not produce any depressive effect on a similar nociceptive flexion reflex in tetraplegic patients with total spinal cord transection.

We will first consider the characteristics of the nociceptive flexion reflex in tetraplegic patients with spinal cord transection. Indeed, the question of whether

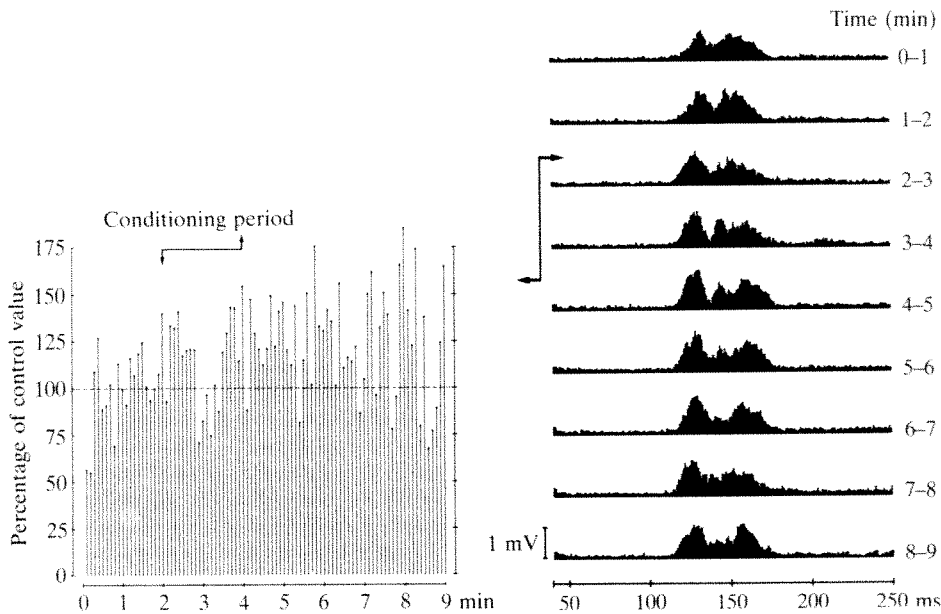


Fig. 4. Individual example of the effects of heterotopic nociceptive stimulation upon the RIII reflex in a tetraplegic patient (presentation as fig. 3).

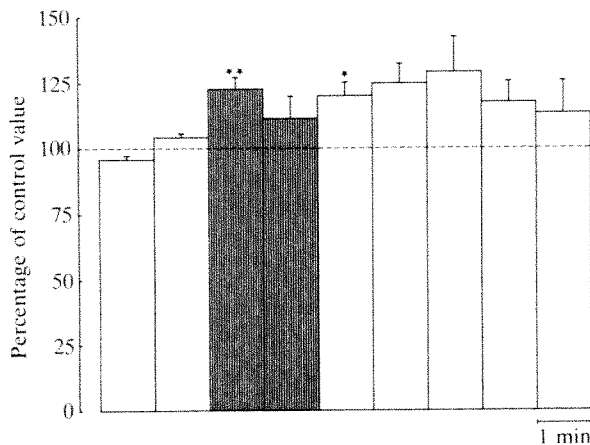


Fig. 5. Mean results obtained with tetraplegic patients before, during (hatched area) and after the nociceptive conditioning period. (Presentation as fig. 4. \*  $P < 0.02$ ; \*\*  $P < 0.01$ ).

the RIII reflex in such patients can be compared to the RIII reflex in normal subjects is a prerequisite to further discussion. In these patients the threshold ( $9.8 \pm 4.9$  mA) and latency ( $119 \pm 7.4$  ms) of the RIII reflex were very similar to the threshold ( $9.2 \pm 2.6$  mA) and latency ( $112 \pm 9$  ms) of the RIII reflex observed in normal subjects. These values were comparable to those obtained in previous experiments (Willer *et al.*, 1984; Willer, 1985). In view of these similarities, it

therefore seemed reasonable to compare the effects of heterotopic nociceptive conditioning stimulation on the RIII reflex in the patients and the normal subjects.

We will next consider the depression of the RIII reflex induced by the nociceptive conditioning procedure. In normal subjects these inhibitory effects appear to be related exclusively to the nociceptive components of the heterotopic stimulation since conditioning stimuli which elicited tactile sensations did not produce any depressive effects.

The nociceptive conditioning stimuli applied to the fingers were clearly painful, as was reported by the normal subjects. Interestingly, the painful sensation was of a 'pin prick' type and was associated with burning and squeezing sensations which were reported as originating from deep structures. In a previous study (Willer *et al.*, 1978), it was shown that stimulation of the sural nerve with 30 mA, 1 ms rectangular pulses activates at least two groups of cutaneous fibres, namely the  $A\alpha\beta$  and the  $A\delta$  groups. In the present work, it seems probable that similar stimuli applied through ring electrodes around the fourth and fifth fingers of the hand activated the  $A\alpha\beta$  and  $A\delta$  fibres of the cutaneous interdigital branches of the ulnar nerve, since the subjects reported a painful pin prick type sensation around the electrodes, projecting into the digital receptive field of the nerves, that is, into the tips of the fourth and fifth fingers. In addition, it is likely that the 30 mA, 1 ms conditioning stimulus also activated some unmyelinated C fibre afferents from the skin and underlying tissues since burning and squeezing pains were reported by the subjects. Such sensations have been found to be mediated mainly via C fibre afferents (Van Hees and Gybels, 1972; Gybels *et al.*, 1979; Torebjörk *et al.*, 1984). Such a stimulus was found strongly to depress the RIII reflex. This finding is consistent with previous work (Willer *et al.*, 1984) in which we showed that the thresholds of both pain and the RIII reflex elicited from the sural nerve were increased when the contralateral hand was subjected to nociceptive stimuli, namely immersion in a 44–47.5° C waterbath or muscular exercise during ischaemia. Since identical results were obtained by applying a painful pinch to the nasal septum, it can be concluded that heterotopic noxious stimuli, whether electrical, thermal, chemical (metabolic) or mechanical in nature, strongly inhibit the RIII reflex.

It is also important to note that in the present study we observed that the depressive effects outlasted the short (2 min) conditioning period by several minutes. From a clinical standpoint, these results may provide a neuronal substrate for analgesia or hypalgesia induced by intense somatic electrical stimulation applied to areas remote from the painful locus (Melzack, 1975; Jeans, 1979). For instance, analgesic effects produced by acupuncture (Mann, 1974; Fox and Melzack, 1976a, 1976b; Melzack *et al.*, 1977; Melzack, 1984) or electroacupuncture (Andersson *et al.*, 1973; Eriksson and Sjölund, 1976; Shanghai Acupuncture Anesthesia Coordinating Group, 1977) frequently employ intensities of stimulation strong enough to induce an unpleasant sensation reminiscent of pain; these procedures result in a widespread distribution of pain relief characterized by long-lasting after-effects.

In tetraplegic patients, the nociceptive conditioning stimulation of the fourth

and fifth fingers did not produce any depression of the RIII reflex. In contrast, the conditioning stimulation gave rise to an enhancement of the reflex, significant during the first minute of its application and during the first minute after its cessation. It is clear that this enhancement of the RIII reflex is purely of spinal origin since both the conditioning (ulnar) and the test (sural) afferent volleys reached the spinal cord below the level of the spinal lesion.

The possible mechanisms of this effect will not be considered in detail here since they seem likely to be related more to the intersegmental coordination of movement than to spinal integration of nociceptive messages involved in sensory processes. They might in fact be related to the propriospinal cervicolumbar pathways which have been repeatedly studied in high spinalized (C1–C3) cat since their initial description by Lloyd and McIntyre (1948). For example, it has been demonstrated that stimulation of all types of brachial afferents except Group I fibres can activate propriospinal pathways to the lumbar spinal cord (Jankowska *et al.*, 1973, Lloyd and McIntyre, 1948, Schomburg *et al.*, 1978). At the lumbar level, activity in these propriospinal pathways can induce a direct monosynaptic excitation of flexor and extensor alpha motoneurons (Schomburg *et al.*, 1978) and disynaptic excitatory or inhibitory actions through convergence onto interneurons activated by muscle Group I or flexion reflex afferents (Jankowska *et al.*, 1974); such effects were found to be reduced when the brachial stimulation frequency reached 4 Hz (Schomburg *et al.*, 1978). In normal human subjects, Meinck and Piesiur-Strehlow (1981) showed that brachial nerve stimulation induced an initial depression followed by a subsequent facilitation of tonically active flexor and extensor muscles, probably via propriospinal pathways. These data are consistent with our observation of a slight enhancement of the RIII reflex in tetraplegics by the nociceptive conditioning stimuli.

The major finding in tetraplegic patients however, was the inability to trigger any inhibitory effects on the RIII reflex with a clearly nociceptive stimulus. The question thus arises as to whether the structure responsible for the RIII reflex depression in normal subjects is of supraspinal origin. Before reaching this conclusion a possible role of the propriospinal interneurons contributing to interlimb coordination has to be considered since these neurons, which are located in the cervical enlargement, can either be damaged or isolated from the lumbar segments in tetraplegic patients. Schomburg *et al.* (1978) have in fact shown that in the high spinalized cat, excitatory or inhibitory brachiolumbar influences are mediated via propriospinal interneurons lying in the lower spinal cord: accordingly, a spinal transection at C5 level slightly reduced but never suppressed (or reversed) these brachiolumbar effects. If these data obtained in the cat apply in man, propriospinal neurons may participate in the effects observed in normal subjects, but it appears very unlikely that they entirely mediate the strong RIII reflex depression that we observed.

Thus our data suggest that a complex loop, ascending from and descending to the spinal cord, is brought into play when a noxious stimulus is applied. In our



previous paper (Willer *et al.*, 1984), we presented arguments to support the idea that such inhibitory processes observed in man share common mechanisms with 'Diffuse Noxious Inhibitory Controls' (DNIC) which, in the rat, affect convergent neurons recorded in the spinal dorsal horn or the trigeminal nucleus caudalis (Le Bars *et al.*, 1979*a, b*, 1982, 1986) and flexion reflexes elicited by activation of high threshold afferents in the sural nerve (Schouenborg and Dickenson, 1985). The present data represents a key finding since DNIC are observed in intact animals but disappear in C1 spinalized animals (Le Bars *et al.*, 1979*b*; Cadden *et al.*, 1983). In addition, an important feature of DNIC is that long-lasting after-effects are often observed; this further underlines the similarity between our observations concerning the RIII reflex in man and the properties of dorsal horn convergent neurons in the rat.

We have demonstrated that the signals responsible for DNIC in animals are transmitted via the ventrolateral quadrant and the dorsolateral funiculus as ascending and descending pathways, respectively (Villanueva *et al.*, 1986*a, b*). If, as seems likely, our present results have something to do with a DNIC circuitry in man, then the clinical and neurophysiological investigations of descending inhibitory pathways modulating the spinal transmission of nociceptive information could be considered in patients affected by various neurological disorders.

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# INTRANEURAL MICROSTIMULATION IN MAN

## ITS RELATION TO SPECIFICITY OF TACTILE SENSATIONS

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### SUMMARY

Recent advances in knowledge, and controversy, concerning cutaneous mechanoreception are reviewed. In particular, the question of *perceptive specificity* is discussed in the light of new experimental approaches, namely microneurography and microstimulation of identified tactile units from the glabrous skin of the human hand. Additional data are also presented. It is concluded that the human brain has an exquisite capacity to detect, localize, delineate, and classify sensations from the input of individual tactile units in the glabrous skin of the hand. The physiological specificity of low-threshold mechanoreceptors in the hand, which has been well documented in previous studies, can now be linked to distinct attributes of very simple tactile sensations which subjects report when a single afferent is stimulated electrically through an intraneural microelectrode.

This conclusion does not conflict with the concept that the brain normally makes use of temporal and spatial patterns of impulses from a large number of receptors of various types to form more complex tactile percepts, such as in the recognition of texture, but the microstimulation data demonstrate that particular patterns of nerve impulses are not a necessary determinant of the subjective quality attribute of a simple tactile sensation. On the contrary, the sensations elicited by a train of impulses in a single afferent unit are remarkably distinct and well characterized in a number of respects. A further conclusion is that the afferent inputs are processed differently in tactile subsystems. This observation warrants caution in generalizing results from one system into a common theory of the origin of sensory modality.

### INTRODUCTION

The enigma of specificity in cutaneous sensation and the role of specific components of the primary afferent message in determining the subjective quality of somatic sensation continues to spur controversy. In 1962, Melzack and Wall published a review 'On the nature of cutaneous sensory mechanisms' in which they presented an alternative formulation to the 'specific-modality' theory of von Frey (1895) and the 'pattern' theory of Weddell (1955) and Sinclair (1955). Melzack and Wall (1962)

suggested that 'Skin receptors have specialized properties for the transduction of particular kinds and ranges of stimuli into patterns of impulses rather than modality-specific information', leading to their conclusion that 'To ram receptors into one of a number of preconceived separate categories would be arbitrary and artificial' (Melzack and Wall, 1962). They did not accept any fixed relationship between sensory unit specialization and perceptual response. They concluded that somaesthetic sensory qualities would be determined 'by particular nerve impulse patterns coursing through widespread portions of the brain'. They proposed that 'more than one fibre carrying single nerve impulses is essential for central cells to detect the characteristics of a sensory stimulus'. Furthermore, they proposed that 'every discriminably different somaesthetic perception is produced by a unique pattern of nerve impulses'. Melzack and Wall's propositions were based on assumptions rather than experimental evidence, and they conceded that 'knowledge of how this occurs is meagre'. Their hypothesis could not be tested at that time, since there was 'no evidence that stimulation of a single fibre in isolation gives rise to a sensation of any kind, and until the experiment is done it is impossible to say what the results will be. To stimulate a single fibre in an intact human subject, to prove satisfactorily that only that fibre and no other has been stimulated, and to record a meaningful sensory judgement is an almost incredibly difficult technical feat, and it will be a long time before unequivocal evidence can be obtained' (Sinclair, 1967).

Torebjörk and Ochoa (1980) and Vallbo (1981) independently claimed to have met the stipulation of Sinclair when they combined *microneurographic recordings* from single sensory units in intact human nerves with *intra-neural electrical microstimulation* of these same units. The data indicated that stimulation of mechanoreceptor units with myelinated fibres, innervating the glabrous skin of the human hand, evoked distinct sensations whose qualities were typical for sensory unit type. Furthermore, changing the pattern of pulse stimuli did not change the basic quality of the evoked sensation. These results were confirmed and expanded in subsequent reports (Ochoa and Torebjörk, 1983; Schady and Torebjörk, 1983; Schady *et al.*, 1983 *a,b*; Vallbo *et al.*, 1984). In one report published in *Brain*, it was stated 'The findings directly refute one of the basic predictions of the pattern theory ... that more than one afferent fibre must be excited for the qualitative characteristics of a sensory stimulus to be defined perceptually (Melzack and Wall, 1962)' (Vallbo *et al.*, 1984).

In response to such a challenge to Melzack and Wall's propositions, Wall and McMahon (1985) found it 'necessary to examine the (microneurographic) recording and stimulation techniques critically to judge their power to provide the required data'. The result of this examination appeared in a critical review published in the journal *Pain*. Wall and McMahon did not themselves undertake microneurography recordings or intra-neural microstimulation (Wall and McMahon, personal communication, 1984). Instead they raised a number of theoretical objections. Their criticism concerned technical and conceptual issues.

1. They assumed that mechanical trauma from the intra-neural electrode would

|            |                                     | Receptive fields                 |                                                      |
|------------|-------------------------------------|----------------------------------|------------------------------------------------------|
|            |                                     | Small,<br>sharp borders          | Large,<br>obscure borders                            |
| Adaptation | Fast,<br>no static<br>response      | <b>FA I</b> (RA)<br><br>Meissner | <b>FA II</b> (PC)<br><br>Pacini and<br>Golgi-Mazzoni |
|            | Slow,<br>static response<br>present | <b>SA I</b><br><br>Merkel        | <b>SA II</b><br><br>Ruffini                          |

FIG. 1. Four different types of tactile afferent units are present in the glabrous skin of the human hand. The figure displays some of the distinguishing physiological properties, the notations, and the anatomical type of end organs in the skin (modified from Johansson and Vallbo, 1983).

cause impulse conduction block in many fibres surrounding the one being explored. Such pressure block, by filtering out an ongoing 'afferent barrage', would allegedly disturb central processing sufficiently to render artificial the sensation evoked by intraneural microstimulation.

2. Stimulus intensities employed during intraneural microstimulation were in their view huge and outside the range accepted for single fibre excitation. Hence sensations evoked by intraneural microstimulation at liminal intensity for detection would be likely to derive from coactivation of many nerve fibres.

3. The psychophysical methods applied to estimate subjective sensory qualities evoked by intraneural microstimulation would be biased in favour of 'specificity'. Thus they questioned the claim that subjective quality of sensation matched the type of stimulated and recorded unit.

4. The remarkable degree of spatial coincidence reported between unitary receptive field and the location of the corresponding sensation evoked by intraneural stimulation was, in their opinion 'not supported by the data'.

By elaborating on these four objections, Wall and McMahon concluded that the published data on intraneural microstimulation did not support the claim that excitation of certain kinds of single sensory units innervating the human hand evokes sensations endowed with specific attributes. Instead, they argued that those same published data supported the modified pattern theory as presented by Melzack and Wall (1962).

We do not agree with this interpretation of our data and will present experimental data which support our conclusions regarding specificity of elementary tactile sensations and contradict some of the general and experimentally unsupported propositions made by Melzack and Wall (1962) and by Wall and McMahon (1985). It is important to emphasize that our data were obtained from experiments performed in cutaneous fascicles of the median or ulnar nerves supplying the

glabrous skin area of the human hand; we have not attempted to extrapolate our interpretations to other regions of the body. Furthermore, these data concerned mainly single low-threshold mechanoreceptor units with large myelinated fibres. We have not formally reported on other types of single sensory units and have not claimed that unmyelinated fibres were stimulated in isolation. Indeed, in their first report Torebjörk and Ochoa (1980) stated 'Although excitation of C fibres ... has usually aroused conscious sensation, it is difficult to ascertain whether the percept is induced by one or several units'. Thus the issues to be discussed relate to low-threshold mechanoreceptive units with large fibres supplying the glabrous skin region of the hand. Four types of such mechanoreceptor units have been identified in this region (fig. 1) (Knibestöl and Vallbo, 1970; Knibestöl, 1973, 1975; Johansson, 1978; Vallbo and Johansson, 1984). Two types, FA I and FA II, are fast adapting in the sense that the units are firing only in response to moving stimuli. These units have previously been called RA (rapidly adapting) and PC (pacinian corpuscle) units but there are good reasons to abandon these illogical terms (Vallbo, 1984). The nerve fibres are probably connected to Meissner corpuscles and paciniform nerve endings, respectively (Johansson and Vallbo, 1979b; Vallbo and Johansson, 1984). SA (slowly adapting) units continue to fire also when a stimulus is held constant. SA I units are morphologically associated with Merkel cell neurite complexes, and SA II units with Ruffini nerve endings (Iggo and Muir, 1969; Chambers *et al.*, 1972; Johansson, 1978).

#### TECHNICAL ASPECTS

##### *Microneurographic recording*

There is widespread agreement that impulses in single afferent nerve fibres, both myelinated and unmyelinated, can be recorded by means of percutaneously inserted tungsten microelectrodes in humans, however unlikely this may have appeared a priori. Wall and McMahon (1985) contended that single fibre recordings are only possible if most of the fibres surrounding the exposed tip of the electrode are blocked. In support of this claim they published photographs of guinea pig fibroblasts distorted by our microelectrode in tissue culture. We will therefore examine the extent of possible nerve fibre block and its effect on single unit recording and on the sensations evoked by intraneural microstimulation.

*Multifibre recording.* Anyone who has performed microneurography is aware of the fact that a single unit is never recorded in complete isolation. Impulse activity can be observed simultaneously from a large number of nerve fibres, if they are activated appropriately. Most fibres are out of focus for recording in the sense that the signal-to-noise ratio is fairly low. The waveforms of the multiunit impulses are mainly negative with a small positive phase following the negative deflection. An isolated impulse of this shape is shown in fig. 2A. It is obvious that it is similar to the classical extracellular recording using an electrode close to the regenerative nerve membrane and another remote electrode (Rosenfalek, 1969). These potentials

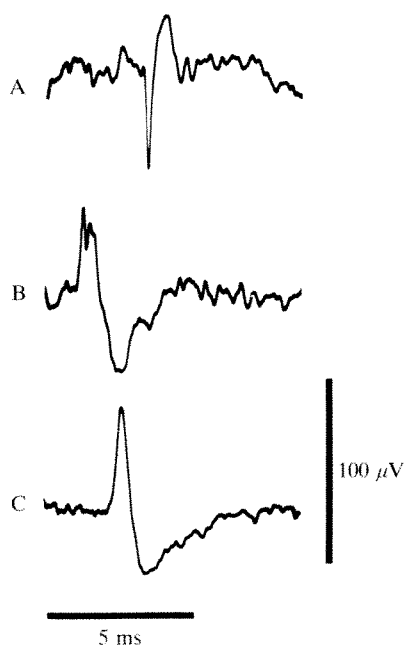


FIG. 2. Waveforms of single impulses recorded with the microneurography technique from large myelinated fibres in human nerves. The waveform illustrated in A is often seen in multiunit recordings and occasionally in single unit recordings from myelinated fibres. The waveforms in B and C are typical for single unit recordings from myelinated fibres (from Vallbo, 1976)

probably represent extracellular recordings of propagated impulses and it may be inferred that they appear when the bare metal of the electrode comes into close contact with the regenerative membrane without causing an injury. The mere fact that in practically all microneurography recordings, it is possible to observe simultaneously action potentials from a large number of fibres, which are capable of impulse conduction, suggests that the 'vast majority of the fibres' are *not* blocked. Moreover, it is a regular finding in microneurography experiments that amount of evoked multifibre impulse activity, as well as the amplitude and shape of impulses, are similar at the beginning and towards the end of an experiment. This would be highly unlikely if the majority of fibres became blocked due to 'continuous back and forth movements of the electrode for up to an hour before a suitable unit can be isolated' (Wall and McMahon, 1985). It should be clarified that, contrary to the assumption of Wall and McMahon, long periods of manipulation are by no means a requirement for single unit recording. Single unit impulses may be obtained very early in an experiment. Thus single unit discrimination is achieved not by elimination of multifibre activity but rather by a selective increase of impulse amplitude from one particular fibre, usually by a factor of two to three, sometimes more, as the fibre is approached by the electrode tip.

*Single unit recording.* The shape of single unit potentials from large myelinated fibres is often different from the multifibre potentials described above. The initial and main deflection is in the positive direction (fig. 2B, C), as expected if the electrode is recording from the interior of the fibre—rather than from the outside—the inward current associated with the rising phase of the action potential produced



in the neighbouring node. This implies that part of the electrode tip has penetrated into the myelin and possibly through the axolemma as well (Tasaki, 1952; Woodbury, 1952). Thus the waveform of single unit potentials from large myelinated fibres indicates that the fibre is injured by the electrode tip (Torebjörk *et al.*, 1970; Vallbo, 1976). The point at issue, then, is whether injury of this nature causes conduction block in the vast majority of fibres within the fascicle, as stated by Wall and McMahon.

This problem was addressed in experiments on exposed cat saphenous nerve in order to explore specifically whether or not the single unit impulses recorded by a microneurography electrode propagate beyond the recording site (Vallbo, 1976). The upper traces in fig. 3 show recordings with gross hook electrodes on the nerve

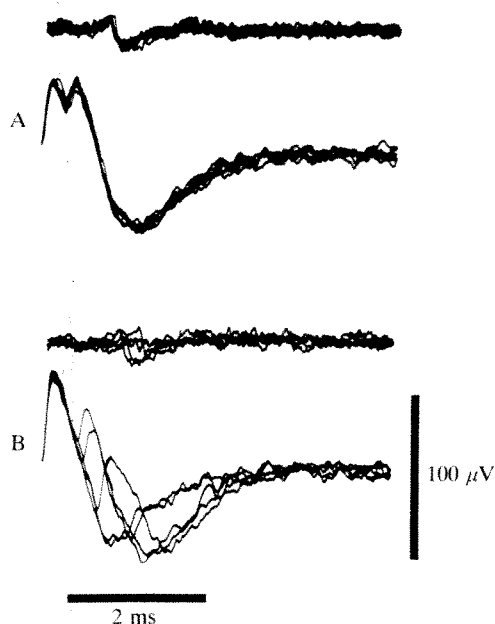


FIG. 3. Superimposed traces of single unit impulses recorded with two electrodes from an exposed cat saphenous nerve. *Upper traces* show impulses recorded with two gross hook electrodes on the nerve, whereas *lower traces* show the same impulses recorded with a microneurography needle electrode inserted in the nerve more distally. Impulses were elicited by a minimal and localized skin deformation on the foot. The oscilloscope was triggered by the rising phase of the lower action potential. *A*, sample records to demonstrate intact impulse propagation in 'partially blocked' single fibres recorded with microneurography electrodes. The conduction delay due to fibre injury, which is evident from the notching of the impulse seen by the microneurography electrode, is not associated with a conduction failure, as claimed by Wall and McMahon. *B*, the development of a conduction block which may occur in a few fibres in the immediate vicinity of the electrode tip is illustrated by the five superimposed recordings.

trunk when impulses were elicited by mechanical stimulation of the skin, whereas the lower traces show concurrent single unit recordings with a microneurography electrode inserted into the nerve. The results illustrated in fig. 3A prove that impulses readily propagate beyond the microneurography recording site in spite of a slight conduction delay which is evident from the notching of the potential. However, a complete failure of impulse propagation also occurred in some of the single units recorded. An example is shown in fig. 3B, illustrating the very process of developing conduction block. It may be seen that three impulses were propagated and two were blocked at the microelectrode. The recordings further illustrate that the block may be predicted from alterations of the potential waveform as recorded by the microelectrode.

Wall and McMahon acknowledged the above work by Vallbo (1976) but misconstrued it in support of their thesis. They interpreted Vallbo's paper as showing 'that 71% of the myelinated fibres ... were completely or partially blocked' and that this was true for 'the fibres in the best possible state'. What Vallbo concluded was rather the opposite, that is, that approximately 80% of the single human units propagated impulses without block during the whole or part of the observation period. Moreover, Vallbo examined those fibres which were not in the *best* possible state as claimed by Wall and McMahon, but in the *worst* possible state since they were situated in the immediate vicinity of the electrode tip and therefore would be most subjected to pressure. It is not clear on what basis Wall and McMahon reached the conclusion that 71% of the fibres were blocked, but apparently they included the units which exhibited a slight conduction delay or 'partial block', as they termed it. This is, of course, misleading because it gives the reader the erroneous impression that impulses in 'partially blocked' fibres do not reach the spinal cord whereas, in fact, these impulses conduct all the way although they are delayed by a few milliseconds. Thus Vallbo's data do not support Wall and McMahon's contention that massive block and 'loss of afferent barrage' prevails in micro-neurographic experiments.

Wall and McMahon also made the mistake of claiming that 'partial fibre block' would help single unit recording by limiting the number of recordable fibres. However, as shown in fig. 3, even when 'a partial block' is present in a fibre the electrode continues to record its impulses (Vallbo, 1976). The simple explanation is that the partial block produced by the tungsten needle is strictly localized and a node adjacent to the recording site produces the amount of current required for a recordable deflection. This is clearly seen in fig. 3B where two impulses failed to propagate but still produced large deflections recorded by the microneurography electrode.

Wall and McMahon argued that single unit recording would not be possible even if the electrode tip impales the myelin sheath because '... the bare metal on the outside of the axon would short out the signal as occurs with a leaky patch clamp'. To explain the undoubted success of the microneurographic method to record single unit impulses, in spite of the presumed shunting, they again advance the interpretation that the vast majority of the axons in the region of the electrode are pressure blocked so that only one or a few fibres in the area are capable of conducting impulses. A conduction block, however, would not reduce the shunting. The degree of shunting is dependent on the size of the exposed metal area and the electrical properties of the surrounding tissue and not on the degree of block.

The fact that single unit impulses can be recorded indicates that the electrode tip, although large in relation to the diameters of nerve fibres, is not large enough to short out impulses from individual nerve fibres completely. We do not know whether additional factors are required for single unit discrimination aside from close contact between the bare metal of the electrode and the axon, and a relatively selective stimulation of the receptive field of the unit under study. It may be

speculated that the shunting effect is diminished by the exposed metal area being partly covered by high impedance structures such as connective tissue and myelin. In any event it seems clear that a massive block of impulse conduction in surrounding nerve fibres is not the key factor for decreased shunting and allowing single unit discrimination.

### *Intraneural microstimulation*

Further criticism by Wall and McMahon concerned the results obtained with intraneural microstimulation. They claimed that sensations elicited by this technique are 'highly abnormal because of the considerable temporary deafferentation and consequent loss of afferent barrage', due to conduction block.

*Loss of afferent barrage.* It is easy to demonstrate that the degree of afferent information which may be lost because of the block is small, not only because few fibres are blocked, but also because the spontaneous input from the glabrous skin region is minimal in the first place. Among tactile units there is only one type which exhibits spontaneous discharge, the SA II type. SA II units make up about 19% of the total number of tactile units in the area (Johansson and Vallbo, 1979a). Moreover, not all SA II units are spontaneously discharging—at most 50% (Johansson, 1978). Since only a small fraction of them might be blocked, it follows that the amount of spontaneous afferent input eliminated would be exceedingly small. It is difficult to imagine that this would seriously upset sensory mechanisms within the central nervous system.

In order to establish whether conduction block affects sensations from intraneural stimulation, six experiments were performed on normal subjects who reported their sensations in the presence of an artificially induced nerve block. We produced a conduction block of myelinated fibres by compression-ischæmia in three experiments, and, in another three, a total block of conduction in all fibres was achieved by local anaesthetic (lidocaine) injection. These blocks were made in the forearm, while intraneural recording and stimulation were carried out in the median nerve in the upper arm. Before blocking, microneurography revealed little spontaneous activity, except for regular firing in occasional SA II units, and irregular bursts of impulses typical for sympathetic fibres in skin nerve fascicles (Hagbarth *et al.*, 1972). However, scratching the skin of the hand evoked rich multifibre discharges in mechanoreceptive units. After blocking, the microelectrode still recorded efferent sympathetic discharges, but no response whatsoever to mechanical stimulation of the hand, indicating that the blocks were effective and that the recording electrodes remained in place.

Before the blocks, intraneural stimulation at increasing intensities just above the level for conscious detection resulted in a discontinuous recruitment of qualitatively distinct sensations, which were projected to separate circumscribed areas of the skin (fig. 4A). These sensations appeared at defined stimulation thresholds in a certain sequence, which was highly reproducible for a particular electrode position.

During the blocks, intraneural microstimulation elicited the same sequence of sensations, with identical qualities and projection territories, at the same stimulation thresholds as before the blocks (fig. 4B), except in one test when the electrode position had been accidentally changed.

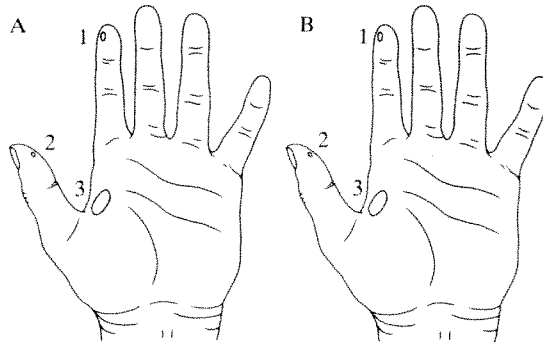


FIG. 4. Recruitment of sensations on microstimulation before and during total nerve block distal to the point of stimulation. A, a gradual increase in stimulus intensity elicited a consistent sequence (1-3) of qualitatively different sensations with distinct electrical current thresholds and separate projection fields before the block. B, no change in recruitment sequence, qualities or projections of thresholds occurred during the block. The qualities of the three sensations were, in 1, pressure, in 2, tapping, and in 3, dull pain.

The experiments show that temporary 'deafferentation' is neither a prerequisite for production of qualitatively distinct sensations, nor does it make these sensations highly abnormal as assumed by Wall and McMahon. We conclude that the sensations evoked by microstimulation in normal human subjects are produced by a somatosensory system which is in a normal physiological state. The attributes of these sensations constitute a firm basis for analysis of the functioning of the somatosensory system in man.

*Current intensity.* Wall and McMahon stated that microstimulation would be unlikely to activate a single fibre selectively because the stimulus intensities used in our studies were too high. In microstimulation experiments in humans the stimulus intensity required to produce a threshold sensation was  $0.81 \mu\text{A}$  (median) (Vallbo *et al.*, 1984). This is, in fact, in excellent agreement with the requirement for selective single fibre stimulation in animals which, by Wall and McMahon's own admission, is of the order of  $1 \mu\text{A}$ . Wall and McMahon supported their criticism by focusing on extreme values and indirect data rather than discussing the most crucial findings. They pointed out that higher current amplitudes emerged if they calculated currents from the data on output voltage and electrode resistance reported in one study (Schady *et al.*, 1983a). Needless to say, such calculations are less accurate than actual measurements of stimulating currents (Vallbo *et al.*, 1984), one reason being that the equivalent circuit of the tungsten needle electrode is not a simple resistance (Vallbo, 1972). Hence a calculation of current from voltage

data cannot be expected to give correct values; such an estimate may at best give the order of magnitude.

Wall and McMahon also made a point of the fact that, in a few cases, we used appreciably higher stimulus intensities to produce the sensations ascribed to single fibre activity. Since the exact spatial and electrical relationships between electrode tip and nodal membrane are not known in the individual trial, the reason why higher stimulus intensities are sometimes required remains unknown. It is conceivable that the precise tip of the electrode might be buried in fascicular connective tissue sheaths or other connective tissue structures, whereas the single fibre to be stimulated makes contact with the bare metal area at a more proximal part of the electrode, where stimulating current density is lower than at the very tip.

We need not rely on speculations to conclude that the stimulus intensity is adequate, because direct proof is available. Data presented in fig. 5 clearly demonstrate that the current range used in microstimulation studies in man does, in

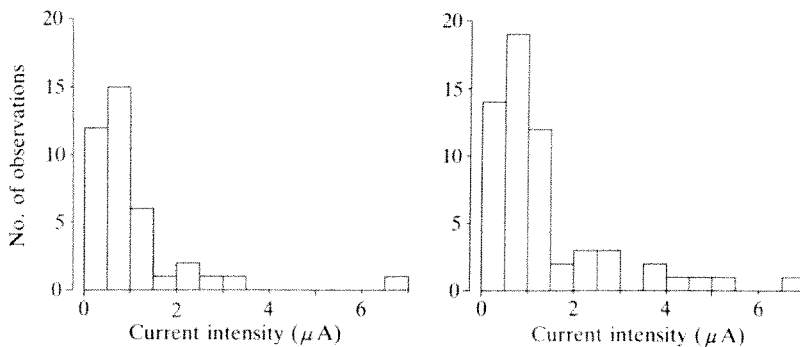


FIG. 5. Liminal current intensity required to produce a quantal response on microstimulation. *Left-hand* histogram shows threshold current intensity for impulses in single nerve fibres of the cat saphenous nerve ( $n = 39$ ; median = 0.70). *Right-hand* histogram shows threshold current intensity for quantal sensations on microstimulation of human nerves ( $n = 59$ ; median = 0.81).

fact, cover the range of currents needed to activate single myelinated fibres in the cat using the same method of stimulation as in man. The proximal end of the cat saphenous nerve was dissected out and placed on silver hook electrodes while a microneurography electrode was inserted more distally in the exposed nerve. Current stimuli were delivered through the needle electrode while nerve impulses were monitored by the hook electrodes. For a number of electrode positions ( $n = 39$ ) the liminal current intensity for exciting a single myelinated fibre was assessed. The results, presented in histogram form in fig. 5A, show that the median intensity was  $0.70 \mu\text{A}$  (quartiles  $0.41\text{--}1.1 \mu\text{A}$ ). For comparison, the data from human nerve stimulation are presented in fig. 5B (Vallbo *et al.*, 1984). The median intensity was  $0.81 \mu\text{A}$  (quartiles  $0.56\text{--}1.45 \mu\text{A}$ ). It is obvious that the current ranges in both studies match very well, supporting the conclusion that one single fibre was activated in

the microstimulation experiments with human nerves. It deserves emphasis that both distributions exhibit a tail at high values, a finding which nullifies Wall and McMahon's argument that multiple fibres necessarily were activated by these stimuli.

*Polarity of current pulses.* Wall and McMahon also claimed that the polarity of stimulating current pulses used in human microstimulation studies indicates that the recorded fibres are blocked. To quote from their review (1985) 'The last body of evidence that stimulating microelectrodes are near to damaged blocked fibres is the statement ... that positive current is more efficient than negative. This of course is the opposite of all classical neurophysiology experience...' We reject the interpretation that the polarity of stimulation would reveal anything whatsoever with regard to conduction block. What the positive polarity indicates is that a part of the bare metal area of the electrode tip has effectively attained a position within myelin. From this position the electrode injects a current into the axoplasm and some of this current leaves the axoplasm through the neighbouring node, which is then depolarized to excitation. Positive pulses being optimal for fibre stimulation is in perfect agreement with our interpretation of the recording situation as discussed above. It also helps to explain why individual nerve fibres can be activated in isolation, since nearby fibres stimulated extra-axonally with positive current will be hyperpolarized and not depolarized.

As we have pointed out in several previous papers, the polarity of the stimulating pulses as well as the shape of the recorded impulses from single myelinated fibres indicate that the electrode has penetrated myelin. In that sense the fibre is injured but this does not allow the conclusion that it is blocked (Tasaki, 1952; Vallbo, 1976).

#### *Conclusions on technical issues*

We have demonstrated that an extensive pressure block is not a feature in microneurographic experiments, although individual fibres may be blocked. A massive block is not present. Moreover, a massive block is not a prerequisite for single unit discrimination or stimulation. Finally, when deliberately provoked, a massive block distal to the electrode has no effect on sensations evoked by intraneural microstimulation. With regard to the stimulus parameters, we have shown that measured stimulus current intensity and pulse polarity used for intraneural microstimulation are optimal for selective activation of single myelinated fibres. It is obvious that Wall and McMahon have underestimated the power of the recording and stimulating technique 'to provide the required data'.

#### CONCEPTUAL ASPECTS

Wall and McMahon (1985) speculated that the sensations which we ascribe to single unit stimulation would either be highly artificial because they assume that

'the bulk of nerve fibres are pressure blocked, or more likely, the brain is abstracting elementary sensations from a diffuse barrage'. We have already discussed and dismissed the first alternative. We shall now discuss their second alternative in relation to available evidence from our experimental data. We will consider several sets of evidence which are consistent with single unit stimulation rather than with coactivation of many fibres. The first set stems from the finding that the tactile sensations reported by the subjects fell into two main categories with distinct attributes, which would be unlikely if a diffuse barrage of impulses accounted for the sensations. The second group of evidence derives from the finding that a gentle increase in stimulation intensity typically recruited successive sensations which had a quantal character. Finally, the most powerful argument for our position originates from the observation that the physiological properties of the individual unit which was recorded matched the psychological characteristics of the sensation reported when microstimulation was applied. We base our conclusions regarding single unit stimulation on the combination of all these sets of evidence.

### *Terminology*

Intraneural stimulation at low intensity was found to elicit quantal sensations which the subjects readily characterized in a number of respects, for example, with regard to quality, temporal profile, and location on the skin. These sensations will be denoted *elementary sensations* (Ochoa and Torebjörk, 1983). The area on the skin where the elementary sensation was felt will be denoted the *projected sensory field* as opposed to the *receptive field* from which a sensory unit can be activated by natural stimuli.

### *Distinct attributes of elementary sensations*

Intraneural microstimulation at threshold intensity for detection induced a limited repertoire of sensations which were usually of a tactile nature. The subjective descriptions of the tactile sensations fell into two main categories, each category being consistent for a particular electrode position as long as the stimulation intensity was kept at threshold level.

In many electrode positions, a pulse train of low frequency gave a sensation of intermittent superficial contact or 'tapping' on the skin. Each tap was felt as a brief event, separated from the next by an interval which seemed equal to the time between pulses in the train. As the stimulation frequency was increased, the repetition rate of subjective tapping also increased and the sensation was often described as 'flutter' at around 20 to 50 Hz and 'vibration' or 'buzzing' at higher frequencies. Thus the temporal profile of the sensation was cyclic and the pulse rate of stimulation was detectable (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983). Interestingly, even a single pulse could often be detected as a single event,

particularly when the sensation was projected to the fingers (Vallbo, 1981; Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984).

A totally different sensation was reported in other electrode positions. It was typically described as a continuous 'pressure', clearly noncyclic and with no trace of intermittency. When the stimulation frequency was increased, the subjective magnitude of sustained 'pressure' increased, without frequency detection (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983). Temporal summation of several impulses was always required for sensory detection of 'pressure' in contrast to the 'tapping' sensation (Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984).

Additional expressions such as 'tickling', 'pulsating', 'stroking' or 'squeezing' were occasionally used. Subjects were sometimes uncertain about the exact quality when high impulse rates (100 Hz) and short trains (0.25 s) were employed (Vallbo *et al.*, 1984) but longer trains and lower frequencies reduced such uncertainty. Allowing for semantics, as well as technical and individual variations, it was striking that most subjects were able to detect clear differences in quality and temporal profile of intermittent tapping as opposed to sustained pressure. Of particular interest was the consistent finding that altering the frequency of stimulation did not convert tapping/vibration into pressure or vice versa, with regard to basic quality, temporal profile or projected field dimensions (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983). The elementary sensations remained as separate entities, one detecting frequency of skin contact, the other detecting magnitude of skin indentation.

With both types of sensation, the projected sensory fields were small, typically 5 to 30 mm<sup>2</sup>, although they were slightly larger for the pressure sensation than for the tapping/flutter sensation (Schady *et al.*, 1983a; Schady and Torebjörk, 1983; Vallbo *et al.*, 1984).

Our conclusion is inescapable: at least two highly specific sensory systems contribute to tactile sensations, and when activated separately each of them elicits distinct sensations which remain independent entities regardless of temporal modulation of the signal pattern. Contrary to what was stated in our papers, Wall and McMahon objected that 'the subjects are trained to describe sensations as one of the 4 categories used to classify afferent fibres'. This calls for rectification, since without training, distinct qualities and temporal profiles of evoked sensations 'were recognizable even for naive subjects in their first exposure' (Ochoa and Torebjörk, 1983). When subjects were instructed to describe the evoked sensations in their own words, many more than four different expressions were used, and yet the descriptions fell into two rather than four main categories, namely intermittent versus sustained tactile sensations. Moreover, different types of multiple-choice questionnaires have been used, allowing for a wide range of sensory categories (Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984). Nevertheless, subjective reports were remarkably congruent in studies performed independently by different research groups in separate laboratories. Finally, the difference in projected field size between tapping/flutter and pressure adds independent support for the cate-



gorization of sensations. It is notable that the subjects were not aware of this difference which was small but statistically significant and found in two independent studies. On all these grounds we refute the claim of Wall and McMahon that the distinct attributes of elementary sensations would merely represent experimental artefacts in favour of 'specificity'. We must accept the separation of sensations into two groups as real and analyse the experimental data further in attempts to explain the findings.

#### *Quantal nature of elementary sensations*

When a sensation first became detectable during intraneural stimulation, it typically remained invariant within a certain current range with regard to quality, temporal profile, subjective magnitude, location, and the size and shape of the projection area. A gradual increase of stimulus intensity above threshold for the first sensation usually lead to the discontinuous recruitment of additional sensations with new and discrete projections, rather than to continuous growth of intensity and projection area of the first sensation. New sensations were therefore abruptly recruited at individual stimulation thresholds, according to the all-or-none principle, and each could be characterized by its specific quality, typical temporal profile and spatially distinct projection area (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983).

We interpret these quantal changes in the evoked sensory experience as the subjective counterpart to electrophysiological recruitment of separate single sensory units. In contrast, Wall and McMahon suggested that spatial summation between several units with overlapping receptive fields accounts for these sensations. They supported their conclusion with a calculation that up to 50 myelinated fibres might be coactivated during liminal intraneural stimulation and that '27 A fibres would need to be coactivated for more than one to have overlapping receptive fields'. It seems obvious that 27 A fibres could not possibly be coactivated at the stimulation intensity we have been using ( $0.81 \mu\text{A}$ ) as shown in a previous section (fig. 5). On the other hand, Wall and McMahon stated that 'the spread of current would be ineffective in activating multiple axons if the presence of the electrode produced a local pressure block in many nearby fibres'. This involves an obvious fallacy of deduction: if Wall and McMahon were right in assuming a considerable conduction block in fibres around the electrode tip, then their favoured explanation for elementary sensations would be highly unlikely, according to their own argument. If many fibres are blocked it would be even more unlikely that our stimulus activated the large set of fibres which Wall and McMahon claimed necessary for the brain to extract a sensation.

To sum up, we reject Wall and McMahon's proposition that 'the brain is abstracting elementary sensations from a diffuse barrage' because measured stimulus intensities are too low to coactive two units with overlapping receptive fields, as calculated by Wall and McMahon themselves. Instead, we maintain that the quantal nature of the sensations is a strong argument for single unit activity being

the basis of the elementary sensations in microstimulation experiments. We do not deny that coactivation of sensory units can occur, even at threshold for sensation, and we have reported criteria to detect such an occurrence (Schady *et al.*, 1983a).

*Matching unit type with quality of sensation*

In microstimulation experiments, the intraneural electrode was switched alternately between stimulation and recording in order to study the relationship between physiological properties of the recorded afferent unit and psychological attributes of the evoked elementary sensation. Striking correspondences were found with two of the four unit types. With regard to quality of sensation it turned out that intermittent tapping/flutter was typically elicited when the largest unit seen by the recording electrode was of the type FA I, whereas sensations of sustained pressure were typically reported with SA I units (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984). The degree of matching in a large material of 172 mechanoreceptor units was highly significant (Schady and Torebjörk, 1983) and held true whichever was established first—sensory unit type or sensation. For FA II units the available materials are small, but it seemed that sensations of vibration or buzzing were associated with stimulation of this type of unit (Ochoa and Torebjörk, 1983; Schady and Torebjörk, 1983; Vallbo *et al.*, 1984). On the other hand, it was striking that no distinct and consistent quality of sensation was related to SA II units (Ochoa and Torebjörk, 1983).

Wall and McMahon explained these findings as the result of personal bias of the experimenters. 'It is important to note that Ochoa and Torebjörk (1983) do not ask whether activity in a single afferent fibre reliably evokes sensation but whether, when using electrical stimuli that do induce sensation, a single fibre of appropriate modality can be recorded at that site'. In fact both strategies have been used in the microstimulation studies, and it was found that some units did not evoke a sensation, in spite of the fact that they were rendered hyperexcitable by the stimulation procedure and hence were *proven* to be stimulated (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983). This was particularly evident for SA II units, but was also found for small proportions of other types of units. It is difficult to explain these observations as a result of personal bias. If, as proposed by Wall and McMahon, an elementary sensation were abstracted by the brain from a multiunit afferent barrage, why should the brain consistently default when that barrage includes an SA II component?

In summary, we have reported that the degree of matching between quality of elementary sensation and unit type is statistically highly significant for two types of units (FA I and SA I), while a significant negative correlation exists for another unit type (SA II). With regard to the fourth unit type (FA II) the material is too small to allow definitive conclusions. These observations argue strongly against Wall and McMahon's contention that 'the brain is abstracting elementary sensations from a diffuse barrage'. Instead, they indicate that certain types of sensory

units induce sensations with distinct subjective attributes when stimulated in isolation.

*Matching unit receptive fields with projected sensory fields*

When the subjects were asked to locate the elementary sensation and define its extent on the skin, they were able to specify the area in several respects, such as location, size, and even shape and orientation. Our results showed that the receptive field for a single unit recording often matched the location of the projected field for the corresponding elementary sensation when intraneural microstimulation was delivered through the recording electrode. Overlapping receptive and projected sensory fields were found in more than 50% of the tests in two independent studies (Schady *et al.*, 1983b; Vallbo *et al.*, 1984). Interestingly, close spatial relationships were found for units which showed a typical correspondence between quality of sensation and unit type. Units which did not conform to this rule had significantly longer distances between receptive and projected fields, suggesting that sensations in these instances were evoked by stimulation of sensory units other than the one recorded from (Schady *et al.*, 1983b).

One of the key theses of Wall and McMahon was that localization of a sensation necessarily depends on the 'greatest coincidence of firing' in many fibres. They questioned the interpretation of our observations since 'projected fields show a variable relationship to single receptive fields'. However, a perfect agreement cannot be expected because the clinical method to test perception of localization that was used in the study to which they refer (Schady *et al.*, 1983b) is associated with a considerable error in point localization (Hamburger, 1980). It is hardly conceivable that this error would be *reduced* if the information made available to the brain is restricted to the input from a single unit. Indeed, the localization error was of the same order of magnitude in the microstimulation experiments as in the clinical setting when local indentation was used (Schady *et al.*, 1983b).

Vallbo *et al.* (1984) employed a different approach to assess spatial matching between the receptive field of the afferent unit and the projected sensory field. They were able to demonstrate that matching was accurate not only with regard to overlap of the two kinds of fields but also in other respects. The size and shape of the reported sensory field agreed well with the corresponding properties of the receptive field. Even the orientation of those receptive fields which were noncircular was found to have correspondence in the subject's sensations so that the subjects perceived the sensations within an area of similar orientation as the receptive field. Such coincidence, which cannot be explained by statistical chance, is a strong argument for the conclusion that the projected 'sensation was actually based upon impulses in the recorded afferent unit being stimulated through the microelectrode' (Vallbo *et al.*, 1984).

In summary, we have reported that projected fields of tactile elementary sensations exhibit a close spatial relationship to the receptive fields of recorded single mechanoreceptor units. This cannot be explained by 'the greatest coincidence of

firing' in many sensory units of any type, as proposed by Wall and McMahon. Instead, the experimental results support our original interpretation that activation of single FA I and SA I units in the glabrous skin gives rise to distinct sensations which are projected with a high degree of accuracy to the receptive field of the stimulated unit.

### CONCLUSIONS

It is obvious that the vast majority of natural sensory experiences depend on information arising from more than one type of primary afferent unit. The issue is not whether signals in two or more types of sensory unit can be integrated centrally to achieve a complex perception. We have never argued against this view. The issue is what sensory experience, if any, would result from the input of just one afferent unit.

Our findings support the view that the tactile modality of the somatosensory system is organized with a high degree of specificity. Indeed the activation of certain types of single mechanoreceptor units innervating the glabrous skin of the human hand constitutes an adequate basis for the construction within the brain of well defined sensations which are specific for unit type. On the basis of these findings we endorse the view that specificity is a key principle for tactile systems. This principle has been supported by strong evidence from other laboratories (Mountcastle *et al.*, 1967; Talbot *et al.*, 1968; Verrillo, 1968) suggesting that populations of mechanoreceptors such as FA I and FA II units contribute to sensations of flutter and vibration, respectively. Wall (1971) countered Mountcastle's conclusions by claiming that they apply only to threshold conditions, that is, to stimuli that are liminal for sensory detection. Our findings eliminate this criticism in that they show modality constancy under suprathreshold conditions, for instance when the stimulation frequency is increased (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984). Furthermore, they allow us to extend Mountcastle's conclusions to encompass the power of a single mechanoreceptor unit to detect and determine the quality, temporal profile and spatial characteristics of a sensation.

Thus our findings firmly connect the activity of one peripheral neural element with a subjective phenomenon and prove the latter's dependence on the input from this element. This is consistent with available anatomical and physiological evidence indicating that modality specificity of mechanoreceptive units innervating the hand is maintained in a topologically organized way throughout the dorsal column nuclear complex, the ventrobasal complex of the thalamus, and the somatic sensory areas of the cerebral cortex (Mountcastle, 1984). To this anatomophysiological apparatus for parallel sensory processing our observations contribute a psychological counterpart in that sensory experience is specific in quality for unit type and is accurate in its projection to the peripheral receptor—at least for certain mechanoreceptor units innervating the hand.

We do not claim that the central processing of afferent signals is confined to the detection and simple summation of qualities and projections of multiple elementary sensations, a view that Wall and McMahon ascribed to us. Clearly, the brain can combine and reorganize temporal and spatial inputs from many afferent units of different types to form more complex precepts than the elementary sensations that we have studied. Needless to say, we have never argued against the interpretation that sensations are influenced by 'a number of factors such as attention, distraction, expectation, immediate and past experience, significance, etc' (Wall, 1971). But we take issue with some of the schematic propositions of Melzack and Wall (1962) which they expand into a general theory of all cutaneous sensations. Since these generalizations resurface in papers by Wall and McMahon (1985, 1986), we must list the contentions which are at variance with views supported by our observations from intraneural stimulation of mechanoreceptor units innervating the hand.

1. 'More than one nerve impulse from a single afferent fibre, or more than one fibre carrying single nerve impulses is essential for central cells to detect the characteristics of a sensory stimulus' (Melzack and Wall, 1962). This generalization does not hold, for instance, for FA I units innervating the fingers, where a single impulse in a single fibre can be sufficient for the brain to detect the characteristics of the stimulus.

2. 'Every discriminably different somaesthetic perception is produced by a unique pattern of nerve impulses' (Melzack and Wall, 1962). To the extent that this generalization concerns quality of sensation and temporal pattern, it does not hold, because a change in temporal pattern of impulses in, say, the SA I system, does not change the basic quality of pressure. Moreover, administering identical patterns to different types of sensory units, for example FA I versus SA I, evokes discriminably different elementary sensations.

3. 'Perceived sensation is not determined in quality and location and time course by the presence of action potentials in uniquely specialised fibres' (Wall and McMahon, 1985). This generalization does not hold for FA I and SA I units. The brain can decode quality, location and time course of sensation from a train of impulses in individual units of those types.

4. 'Threshold of perceived sensation depends not on the presence or absence of impulses in a particular type of fibre but on their achieving certain levels of firing' (Wall and McMahon, 1985). This generalization does not hold, for instance, for single FA I units innervating the fingers (*see above*) but it holds for SA I units, in which temporal summation of impulses is needed for sensory detection.

5. 'The time course of the afferent barrage is poorly related to the time course of perception' (Wall and McMahon, 1985). This generalization definitely does not hold for FA I units, which evoke an intermittent sensation which faithfully replicates the temporal pattern of the stimulus.

6. 'Wide spatial gradients of stimulus and of afferent activity are abstracted by the brain to achieve a perception of apparent elementary sensations with a spot location' (Wall and McMahon, 1985). This generalization holds in the sense that

central mechanisms such as surround inhibition help to sharpen the spatial extent of a tactile sensation. However, it is important to note that spatial summation is not a necessary requirement to locate accurately a qualitatively distinct sensation from FA I and SA I units. Spatial summation may perhaps be a requirement for SA II units to evoke a sensation; at least they do not evoke any distinct sensation when stimulated individually.

One essential conclusion from our findings is that physiological specificity of low-threshold mechanoreceptors in the hand is linked to distinct attributes of very simple tactile sensations. This conclusion does not preclude acceptance of the concept that the brain uses the temporal and spatial patterns of impulses from receptors of various types to form more complex tactile percepts; for instance in the recognition of texture. However, a particular pattern of nerve impulses is not a necessary determinant of the subjective quality attribute of a simple tactile sensation. Another essential conclusion is that the afferent inputs are processed differently in tactile subsystems. This observation warrants caution in generalizing results from one system into a common theory of the origin of sensory modality.

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## THE INTRANEURAL DISTRIBUTION OF MYELINATED FIBRES IN THE EQUINE RECURRENT LARYNGEAL NERVE

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### SUMMARY

The intraneural course of nerve fibres in the equine recurrent laryngeal nerve was investigated by partially ligating the nerve at a proximal site, and 3–8 weeks later, tracing the course and spatial relationships of intact and degenerating fibres along the distal stump. This nerve was chosen because of its great length, the fact that it is a nonbranching motor nerve and because of debate about the course of abductor and adductor nerve fibres in the recurrent laryngeal nerve. Six ponies were used and in each the recurrent nerve was partially ligatured about 20 cm from the larynx, using a fine silk suture. In all there was a clear separation of intact and degenerating fibres just distal to the suture, but they became mixed close to the point of innervation of the laryngeal muscles. The numbers of intact myelinated fibres remained similar along the partially denervated nerve segment. These results suggest that myelinated fibres mix within the recurrent laryngeal nerve and that focal lesions of this nerve should not result in denervation of individual laryngeal muscles.

### INTRODUCTION

The anatomical course of individual nerve fibres within peripheral nerve trunks is a controversial subject. Early workers suggested that nerves resembled cables with nerve fibres separated into discrete fascicles, which proximally contained either sensory or motor fibres (Bardeen, 1906–7; Langley and Hashimoto, 1917). Other subsequent investigators observed the constant union and division of fascicles, forming complex intraneural plexuses within peripheral nerves and concluded that fibres continually mix within the course of nerve trunks (Compton, 1917; Kraus and Ingham, 1920; McKinley, 1921; Goldberg, 1924; Kilvington, 1940; Sunderland, 1945; Sunderland and Ray, 1948; Sunderland and Swaney, 1952). This view of intraneural mixing has persisted until recently. Other dissection studies have shown less intermingling than Sunderland suggested (Jabaley *et al.*, 1980), and the technique of microneurography and single nerve fibre recording has further challenged the conclusion that fibres randomly mix within fascicles (Schady *et al.*, 1983).

Whether there is a proximal grouping of sensory or motor fibres within a nerve trunk has important clinical consequences. If the nerve is partially sectioned at a proximal level, is this likely to produce serious motor or sensory deficits and if a nerve trunk is completely sectioned, how accurately do sectioned fascicles have to be apposed by suture in order to optimize chances for regeneration? The present study has adapted a morphological approach used by Ueyama (1978) to examine whether intraneural mixing of fibres occurs. In Ueyama's study, the course of degenerating fibres in the dog's sciatic nerve was mapped after sectioning certain lumbar or sacral nerve roots. We have devised a technique for partial ligation of the equine recurrent laryngeal nerve (RLN), which results in denervation of a proportion of fibres within the ligatured nerve. Since the equine RLN is a long nonbranching motor nerve, the same population of fibres can be examined over a long distance. If minimal intraneural mixing occurs, the intact and degenerating fibres should remain clustered in discrete regions of the nerve trunk throughout the distal length of the nerve. If, however, nerve fibres intermingle within the distal nerve, the pattern of intact (and degenerating) fibres should appear to be random. In addition to the great length of the equine RLN which made this a viable technique, certain other neuroanatomical questions remain about this nerve, in particular in relation to the course of the abductor and adductor nerve fibres innervating the laryngeal muscles, and the effect that focal nerve lesions might have on laryngeal function. In man, partial loss of function of the vocal folds has been suggested to be due to selective susceptibility of the abductor muscle to denervation (Semon's Law; Semon, 1881). In the horse, the converse is thought to be the case based on morphological evaluation of its intrinsic laryngeal muscles with subclinical denervation of the larynx (Duncan *et al.*, 1974). This study was therefore designed to answer outstanding questions regarding the intraneural mixing of fibres, and in particular the effect that partial lesions of the equine RLN may have on laryngeal function.

#### MATERIALS AND METHODS

Six ponies, all with normal laryngeal movement as determined by endoscopic examination, were included in this study. Each animal was anaesthetized and the right RLN was isolated approximately 20 cm proximal to the larynx through a ventral cervical incision. Using an intraoperative dissecting microscope, a 6-0 silk suture was placed so that an estimated 50% of the transverse section of the nerve could be incorporated in a ligature. Each pony was evaluated daily for any sign of distress and no deleterious effects of the surgery, or respiratory difficulty, were noted. The ponies survived for a period ranging from 3–8 weeks. Each pony was then euthanized with an overdose of barbiturate anaesthesia and the entire extrathoracic lengths of both recurrent nerves, including abductor and adductor branches, were removed and diced in 2.5% phosphate-buffered glutaraldehyde at 4° C. After 24 h fixation the nerves were measured and cut into 1 cm lengths with their proximal-distal orientation maintained. The segments were postfixated in osmium tetroxide, dehydrated through alcohols and embedded in epon resin. Sections 1  $\mu$ m in thickness were cut at each level (15–20 levels per nerve) with a Reichert Ultracut microtome, stained with alkaline toluidine blue and examined by light microscopy.

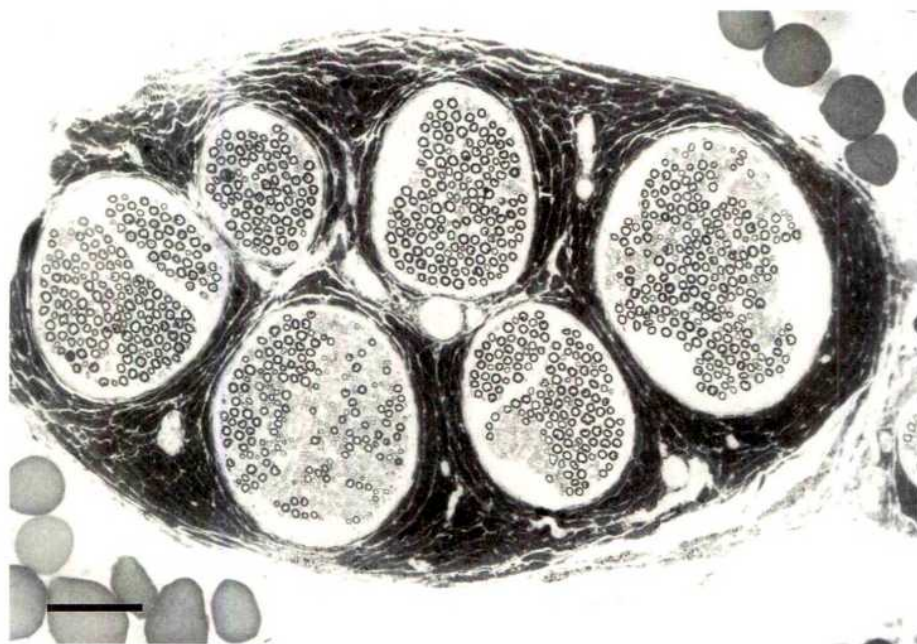


FIG. 1. Normal recurrent laryngeal nerve. Small myelinated fibres which are sensory from the oesophagus and trachea are present in lower two fascicles and on the right. Toluidine blue. Bar = 100  $\mu$ m.

The cross-sectional area of the nerve was divided approximately into four quadrants. The remaining intact myelinated fibres and, where possible, the remnants of those undergoing wallerian degeneration, were identified in each cross section and their location recorded. While it was impossible to trace individual nerve fibres, it was possible to infer intraneural migration of myelinated and degenerating fibres by noting the proportion of fibres in each quadrant at several points distal to the point of suture. To map out the position of these fibres, camera lucida drawings were made of each nerve at 5 cm intervals from the suture site to the larynx. Intact rather than degenerating myelinated fibres were marked, as they could be more accurately identified. These fibres were counted at each of the 5 cm intervals and the results summarized in fig. 5, which shows the total number of fibres just below the suture and at the most distal point from it.

## RESULTS

The right RLN above the site of the ligature was normal in all the ponies (fig. 1), although numerous Renaut bodies were seen in some nerves. Distal to the ligature the number of damaged fibres ranged from about 25 to 75% of the total myelinated fibre population. At the site of ligature and just distal to it, the remains of the suture material was evident (fig. 2A, B). At the ligature site, individual fascicles that contained either intact or degenerating fibres were clustered at either pole of the nerve (fig. 2A, B). Occasional fascicles in the region bordering these areas contained a mixture of fibres (fig. 3A).

The distribution of fascicles, and of myelinated and degenerating fibres, was then followed distally. It immediately became obvious that the total number of fascicles



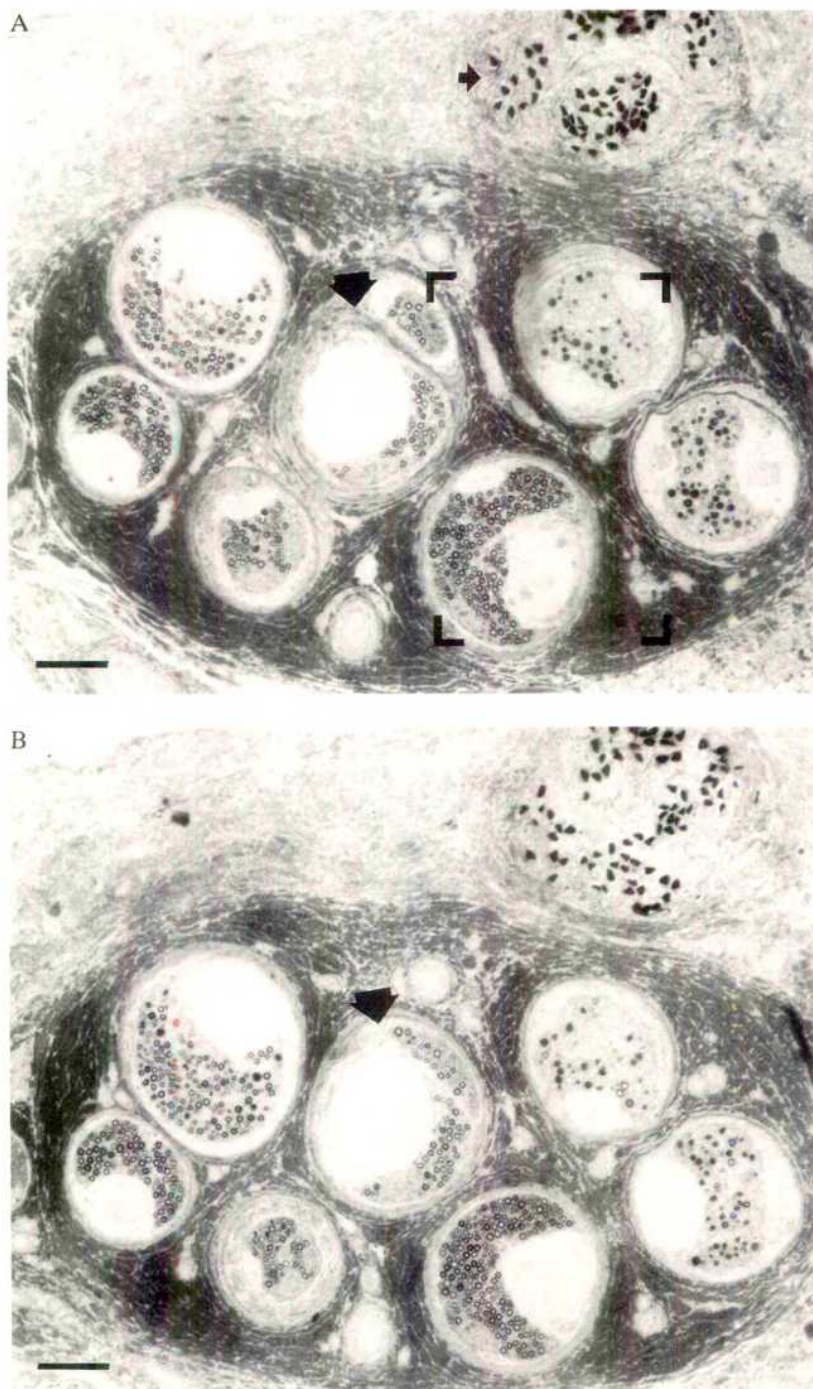
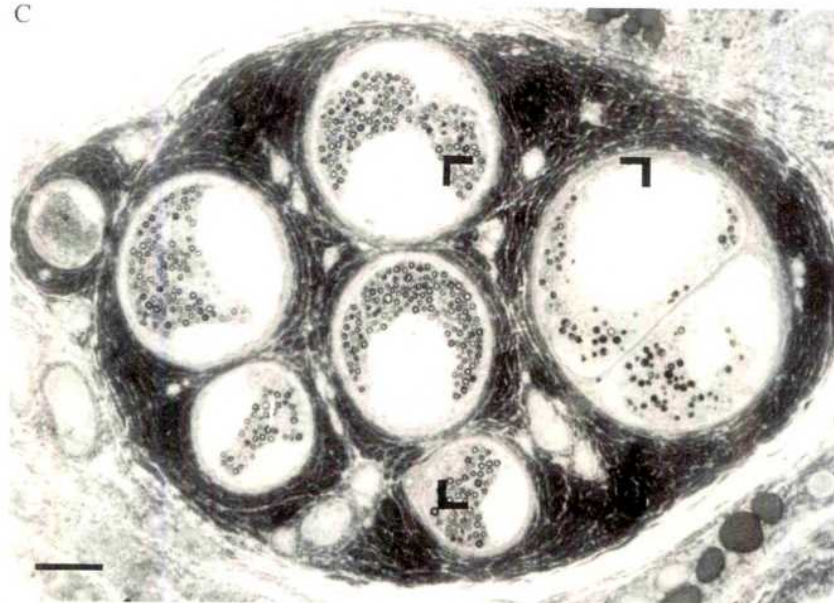
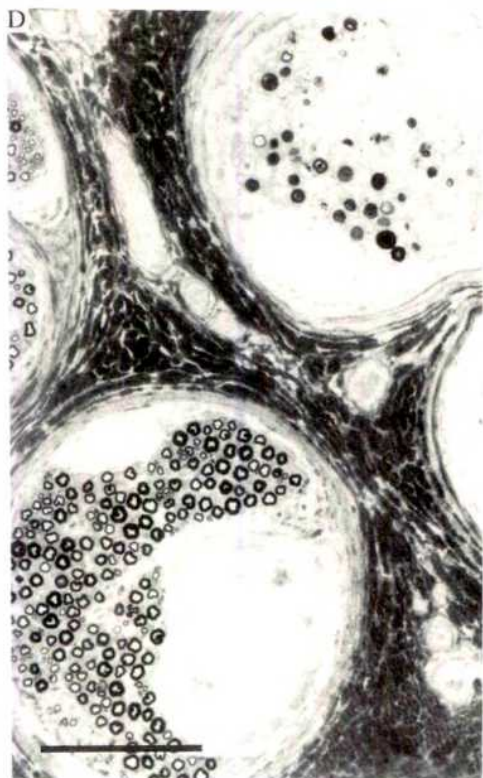


FIG. 2. (Fig. 2C-E on facing page) *Pony D*. A, right RLN just distal to the ligature, a piece of which remains (small arrow). The 2 fascicles on the right contain degenerating fibres but those to the left have only intact fibres. Note the intrafascicular band (large arrow) and the prominent Renaut bodies. Brackets mark area enlarged in D. B, 2 cm distal to A, the fascicle which had an intrafascicular connective band has now been unified (arrow). C, 5 cm distal. The fascicular number has changed but the majority of degenerating fibres are on the right side of the nerve. Brackets mark area enlarged in E. D, enlargement of area from A. There is a clear separation between fascicles with either intact or degenerating fibres. E, enlargement of area from C (marked with brackets). Compared with the clear division of fibres seen in D, by 5 cm distal to the suture one fascicle now contains both intact and degenerating fibres (arrow). All toluidine blue. Bars = 100  $\mu$ m.

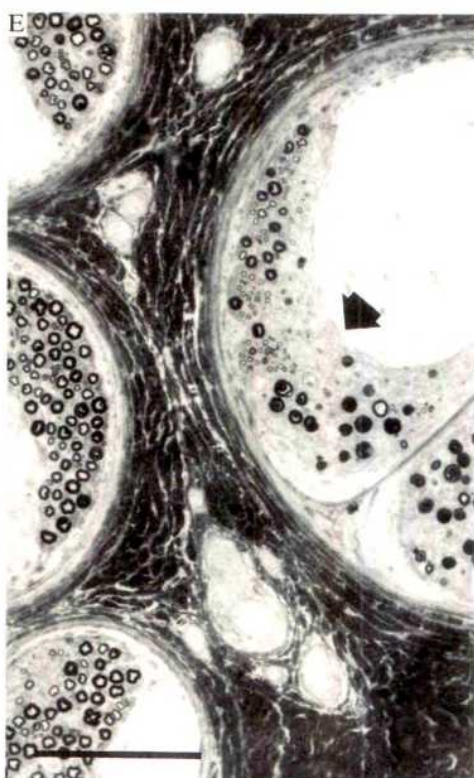
C



D



E





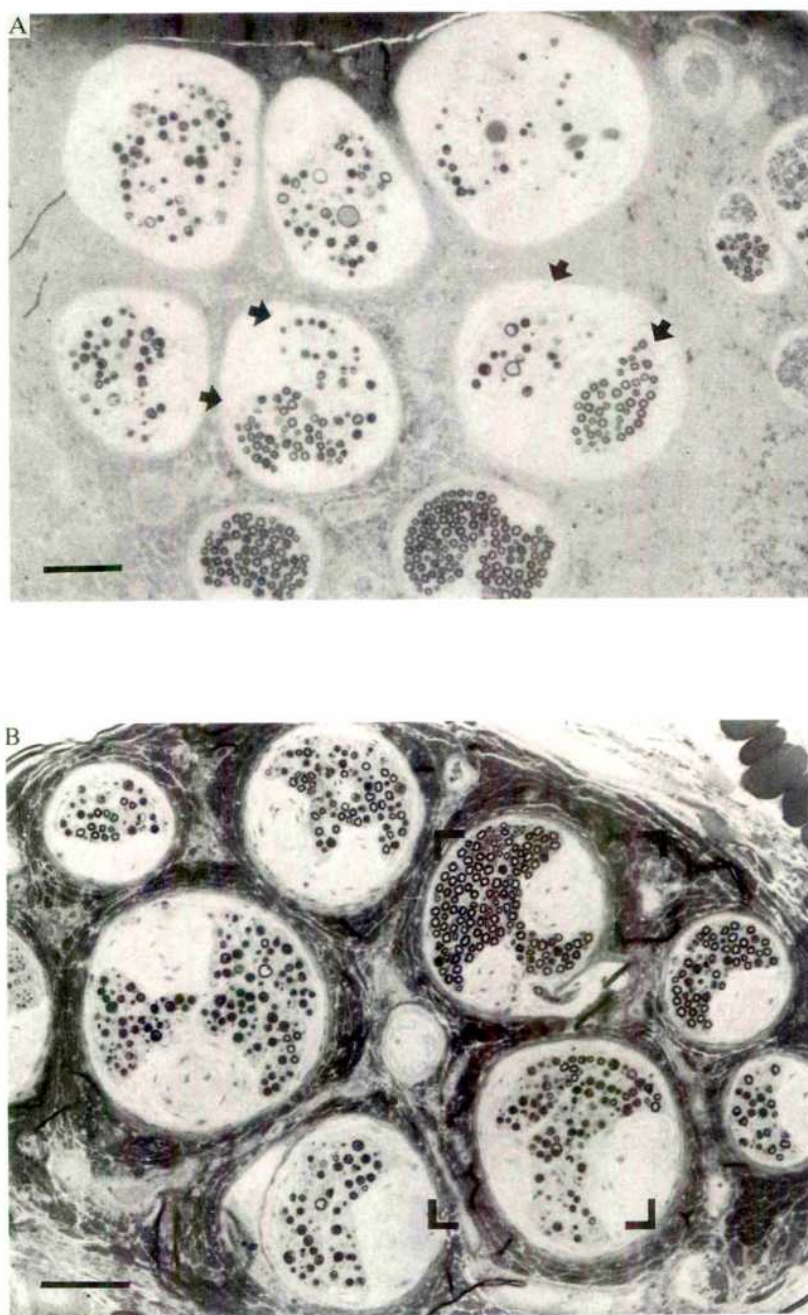
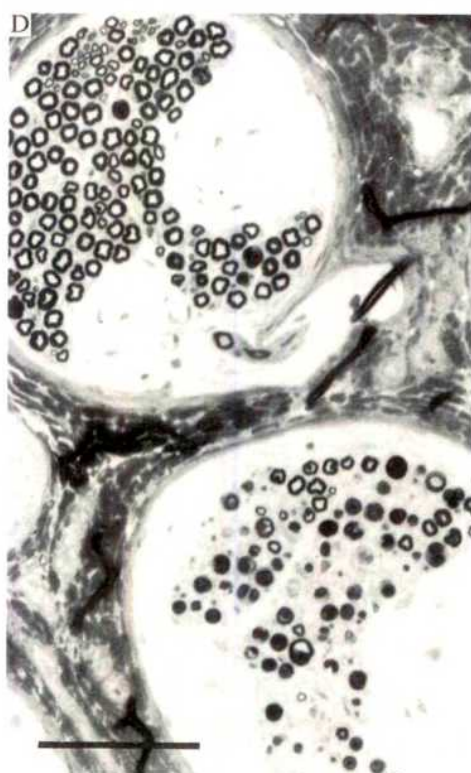
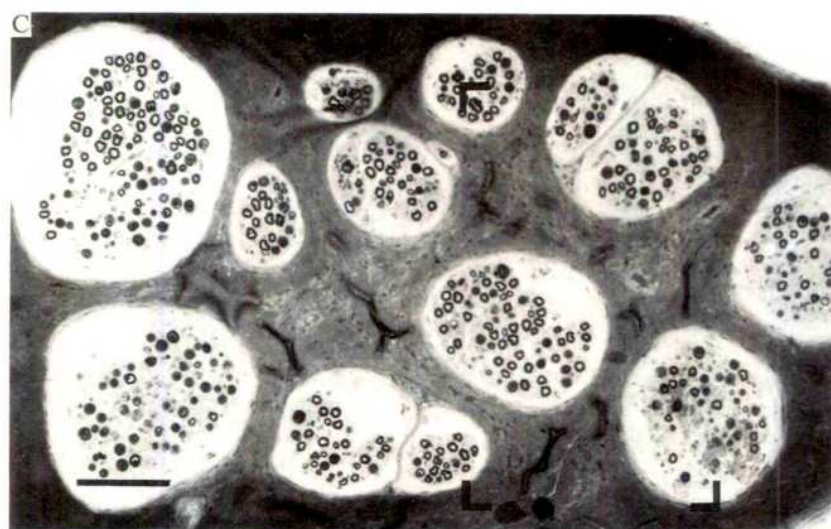


FIG. 3. (Fig. 3C-E on facing page) *Pony C*. A, at the ligature site. Unlike *Pony D* (fig. 2) about 50% of the nerve has been denervated. It also appears that fascicles containing both degenerating and intact fibres are present, although they form separate groups (arrows), in one instance divided by a thin intrafascicular strand. B, 10 cm distal. Intact fibres are mainly seen in the upper quadrant and there appears to be little mixing of fibres. Brackets mark area enlarged in D. C, 20 cm distal. There now appears to be an even mixture of degenerating and intact fibres. Brackets mark area enlarged in E. D and E, higher magnification of areas in B and C, respectively. In D the lower fascicle contains a mixture of fibres, while in E there appears to be a complete intermingling of fibres. All toluidine blue. Bars = 100  $\mu$ m.





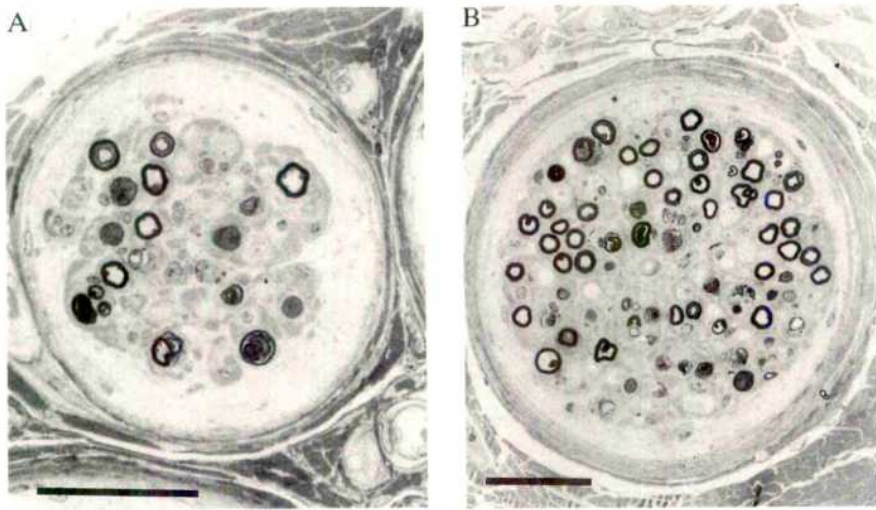


FIG. 4. Pony D. The abductor (A) and an adductor branch (B) of the right RLN. Note that intact fibres, degenerating fibres and areas of fibre loss can be seen in both branches of the nerve. Toluidine blue. Bars = 50  $\mu$ m.

varied along the course of the nerve with union and division of adjacent fascicles (figs 2A, B, 3A, B, C). On average the nerve consisted of 10 fascicles but the loss or addition of as many as 4 fascicles could be seen in adjacent 1 cm sections. The position of fascicles in relationship to each other also varied and it was usually impossible to 'match' fascicular position between segments of the nerve more than 3 cm apart. Despite this minor changing of fascicular position, the transverse section of the nerve could be divided into affected and unaffected areas (as defined by the position of degenerating and intact fibres) for several centimetres.

The first change in position of fibres in relationship to each other was evident approximately 3 cm distal to the ligature site, at which point the fascicular number and organization had also changed (fig. 2C). In one instance, at this point a small group of intact myelinated fibres was found lying adjacent to, but not mixing with degenerating fibres (fig. 2E), indicating an interfascicular rearrangement. The second method of rearrangement of fibres was an intrafascicular spread which apparently, in some cases, resulted in a distal redistribution of fibres. However, this only occurred over a considerable length of the nerve and is illustrated in a second pony (Pony C) at the ligature site, and 10 cm and 20 cm distal to it (fig. 3). At the site of ligature there was no mixing of intact fibres, but by 10 cm intermingling of fibres had started to occur (fig. 3B, D) and at 20 cm there was an even mixing of intact and degenerating fibres (fig. 3C, E). In all 6 ponies intact fibres, myelin ovoids and areas of fibre loss were seen both in abductor and adductor branches in the nerve (fig. 4). In the ponies which survived for up to 8 wks after surgery, signs of fibre degeneration (myelin ovoids) had often disappeared (figs 3A, 4). The distribution of myelin ovoids along the course of the nerve was evaluated to try to determine whether or not there was any spatial orientation to their distribution, that is,



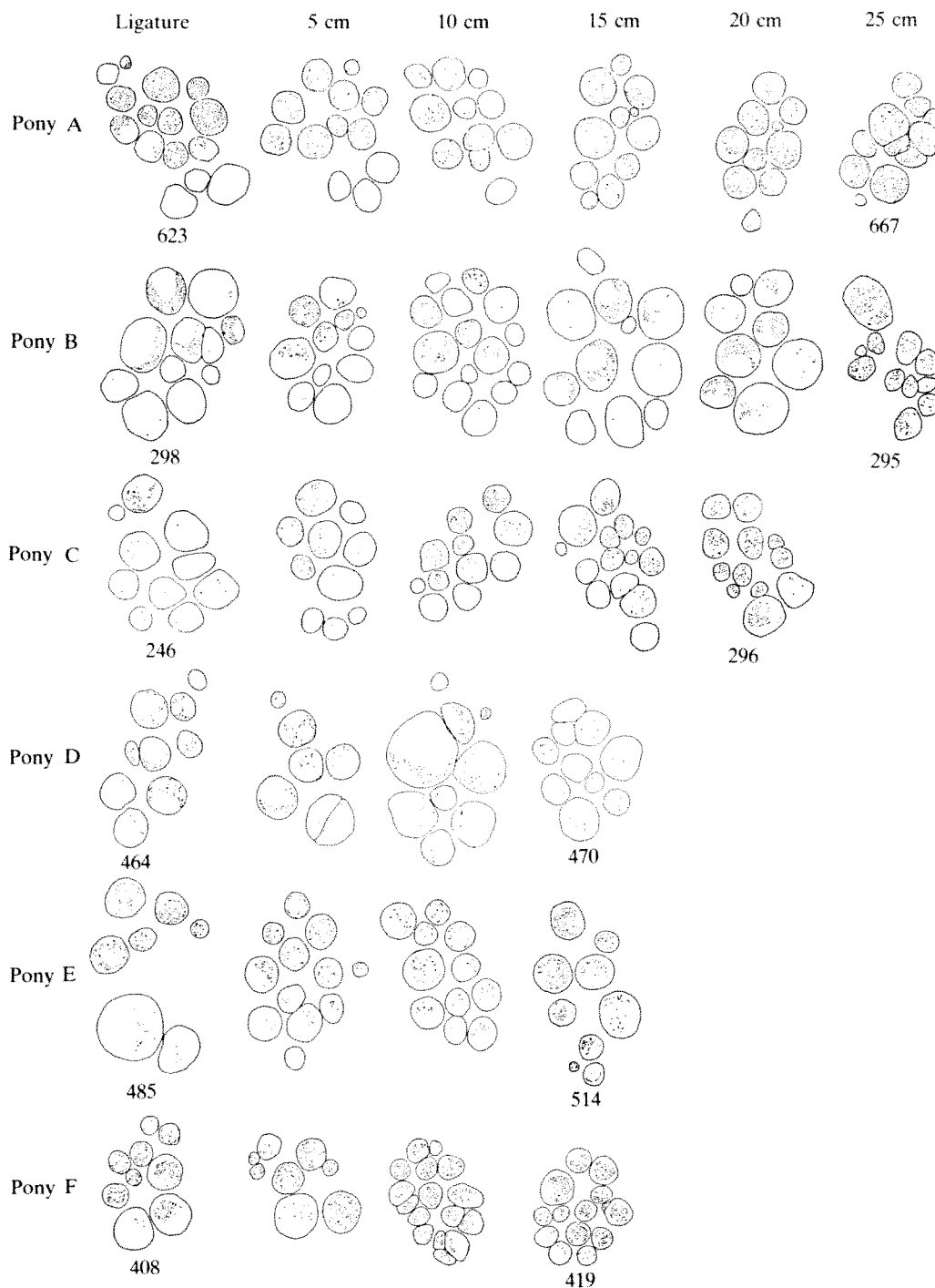


FIG. 5. Montage of the right RLN in all 6 ponies, at the ligature site and thereafter at 5 cm intervals distally, to the point of branching of the nerve into abductor and adductor branches. Intact myelinated fibres are marked as dots and the total number of these at proximal and distal levels is noted below each nerve. The change in numbers and pattern of fascicles is clear. The fascicles which contain no dots had either ovoids or contained only connective tissue and Büngner bands. In nearly all cases there is an eventual distribution of intact fibres into all fascicles with no 'empty' fascicles being seen in the most distal nerve. In some instances (e.g., Pony B), this final mixing only occurs at the most distal point sampled. Survival times: Pony A, 8 wks; B, 6 wks; C, 4 wks; D, 3 wks; E, 4 wks; F, 3 wks.

whether all the nerve fibres entrapped by the suture degenerated synchronously along the entire length of the distal nerve. However, at the earliest time after operation (3 wks), myelin ovoids were seen along the entire distal length of the nerve and so it would have been necessary to examine the nerve at shorter intervals after ligation to determine this.

The pattern of intrafascicular mixing is demonstrated for each pony in the camera lucida drawings of the nerve at 5 cm intervals in fig. 5. While the pattern of redistribution of fibres was not identical in all cases, several points can be made. First, in the majority of cases, mixing is slow to develop and can take up to 15 to 20 cm to occur. Secondly, equal numbers of intact and degenerating fibres in each quadrant of the nerve were found only in ponies in which the nerve was ligated 25 cm from the larynx. In the 3 ponies in which the ligation was placed 15 cm from the larynx this mixing was not as defined as at distal levels.

The left RLN in all the ponies examined was normal with no evidence of nerve fibre pathology. As in the right RLN (figs 2, 3), frequent Renaut body formation was seen. The number of intact myelinated fibres counted between the site of ligation and the distal nerve varied very little in all 6 ponies (fig. 5).

#### DISCUSSION

The technique used to produce the partial denervation of the equine RLN provided a clear-cut separation between intact myelinated fibres and degenerating fibres distal to the suture site. It was therefore possible to judge whether fibres intermingled between the suture site and the larynx. Two sequelae could result following partial nerve suture: (1) at the point of branching of the nerve into abductor and adductor branches, myelinated fibres and degenerating fibres could cluster into distinct populations, or (2) there could be an even mixing of both types of fibres at the branch point, with the abductor and adductor branches containing intact and degenerating fibres. The results clearly show that the latter occurs, but in some instances it took between 10 to 20 cm to develop. Indeed, in the 3 ponies in which the nerve was ligated only 15 cm from the larynx, the final degree of mixing was not as complete as in those ligated 25 cm proximally. This may indicate separation of nerve fibres into muscle groups, beginning at 10 to 15 cm from the larynx. The constant changing of the fascicular architecture, despite the fact that it is a nonbranching motor nerve, also suggested that nerve fibre mixing occurs. Fascicular number often changes and there is frequent division and union of fascicles; this was deduced from the observation that fascicles can be divided by intrafascicular strands of connective tissue and yet the same fascicle, 1 cm above or below this site, appears nondivided. This fascicular change was not affected greatly by fascicles containing sensory fibres from the oesophagus and trachea which join the nerve at different levels. These small fascicles, containing mainly small myelinated fibres, usually remain separate from the major part of the nerve and, if fusion does occur, they are always separable on account of their clustering

and size (fig. 1) (Dyer, 1985). One possible source of error in this experiment could be the presence of regenerating fibres in the distal nerve, originating proximal to the suture, and joining the fascicle distal to it because of the fascicular fusion which occurs. This was thought to be unlikely as there was insufficient time between operation and death for regenerating fibres to travel to the distal portions of the nerve and to appear morphologically mature. Moreover, there was no histological evidence of regenerating clusters. Finally, the counts of myelinated fibres in the nerve distal to the suture and at the most distal point of the nerve in all 6 ponies were very similar.

The results of this study do not entirely agree with the previous studies on nerve fibre mixing, although the techniques used are different. One of the obvious differences between the present technique and the studies in which gross dissection of nerve trunks has been performed is that the latter do not permit the tracing of nerve fibres or groups of fibres (Jabaley *et al.*, 1980). There are similarities, however, between our technique and that used in the study of Ueyama (1978) on the sciatic nerve of the dog and also in some of the conclusions. He showed that there was less intermingling than Sunderland had predicted and that fibres destined to become a terminal muscle fascicle were only separate from the nerve some distance before their departure from the main nerve trunk. This may be similar to our observation that partial ligation of the nerve 15 cm or less from the larynx might in fact denervate a group of fibres which have started to form a specific nerve/muscle branch.

One of the major differences between the present experiment and other studies investigating intraneural mixing is in the selection of the recurrent laryngeal nerve, a nonbranching motor nerve. The fact that it does not have motor branches makes the issue of intermingling of fibres easier to evaluate. Therefore we cannot directly compare our results to those of Schady *et al.* (1983) who carefully evaluated the degree of mixing of muscle and cutaneous nerve fibres in the human median nerve. The difference between our results may stem from the fact that the RLN is not a cutaneous nerve and so the internal anatomy is different. However, there are sensory fibres supplying stretch receptors in these muscles, at least as determined electrophysiologically (Duncan and Baker, 1987), and so motor and sensory laryngeal nerve fibres coexist in the main body of the nerve. In addition, Sunderland and Swaney (1952) also showed that there was considerable plexus formation in the human recurrent laryngeal nerve although, of course, the pathway of individual fibres, or groups of fibres, was not determined. The possibility of a species difference may be entertained but seems unlikely as Sunderland and Swaney (1952) suggested that there was also notable intraneural plexus formation in the human RLN. The chance that the RLN may be different from other long motor nerves has led us to repeat this experiment with phrenic nerve in the horse. Preliminary observations suggest that distal mixing of fibres also occurs in this nerve (I.D. Duncan, D. Smith and R.M. Archer, unpublished observations). Finally, there is evidence from a study of the cat RLN, that after injection of horseradish peroxidase (HRP) into a

laryngeal abductor or adductor muscle, HRP-labelled axons are diffusely spread throughout the nerve (Malmgren *et al.*, 1977). This suggests that there is no grouping of nerve fibres supplying either set of muscles in the cat RLN.

A second reason for undertaking these experiments was to determine whether or not an old 'law' of human laryngology (Semon's Law; Semon, 1881) which states that the abductor muscle of the larynx is preferentially denervated in partial lesions of the RLN, could be applied to the equine RLN, that is, could focal traumatic or compressive injury to this nerve result in selective denervation of the equine larynx and hence loss of either abduction or adduction of the vocal fold? Since Semon's conclusion, the majority of investigators have tended to disbelieve this statement, but most of the counter-evidence comes from endoscopic examination of patients with vocal fold paresis and interpretation of vocal fold position. Indeed in the horse, the opposite may exist. In the horse's larynx, partial lesions of the RLN result in preferential atrophy of the adductor muscles and the abductor muscle is often spared or only minimally denervated (Cole, 1946; Duncan *et al.*, 1977; Cahill and Goulden, 1986; I.D. Duncan, J. Amundson, R.L. Sufit and P.C. Cuddon, unpublished observations. This can lead to loss of or poor vocal fold adduction in the presence of normal abduction. The results of the present study, however, would suggest that this would only occur following a partial lesion to the RLN if this happened in the very distal nerve (i.e., within 10–15 cm from the larynx). More proximal lesions, for example in the mediastinum or at the level of the aorta, should affect all fibres equally. In the population of horses with subclinical laryngeal paralysis, the propensity of adductor muscle fibres to be denervated may relate to other factors such as the overall length of the nerve supply or the size of nerve fibres to the individual laryngeal muscles, and the role that this may have in a distal axonopathy.

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# THE DOUBLE DISSOCIATION OF SHORT-TERM MEMORY FOR LISTS AND SENTENCES

## EVIDENCE FROM APHASIA

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### SUMMARY

We document the sentence and list repetition skills of 3 aphasic patients. Cases 1 and 2 were classified as span-impaired conduction aphasics and Case 3 was classified as a span-preserved transcortical sensory aphasic. We found that repetition by the span-impaired cases was facilitated by increasing the 'meaningfulness' of lists, whereas this had no effect on the performance of the span-preserved case. The patients' ability to repeat sentences was contrasted with their ability to repeat three words contained in the sentences, and a double dissociation was obtained: the span-impaired cases were better at repeating sentences than in repeating three word lists whereas the span-preserved case showed the opposite pattern of difficulty. The repetition of sentences containing a known and unknown vocabulary was tested in the span-preserved case. His repetition of sentences containing words which he still knew was significantly better than his ability to repeat sentences containing a vocabulary of words which he had 'forgotten' as a consequence of his aphasia. The patients' ability to repeat complete, incomplete, and nonsense sentences was contrasted: overall the span-impaired patients were somewhat better at repeating complete sentences than incomplete sentences. Finally we examined the patients' ability both to comprehend and repeat word strings in an abbreviated 'naming from description' task: the span-impaired patients were able to comprehend three word strings, but unable to repeat them, the span-preserved case was able to repeat but not comprehend. On the basis of these double dissociations we conclude that the evidence indicates two dissociable short-term memory systems, one a relatively passive phonological store subserving list repetition, the other a dynamic, anticipatory, and integrative memory system which underpins sentence repetition.

### INTRODUCTION

The selective preservation or impairment of word or digit repetition is a defining feature of the two classical aphasic syndromes, transcortical aphasia and conduction aphasia. In transcortical sensory aphasia, repetition of single words and word lists is preserved despite there being a marked comprehension impairment. Furthermore in the class of transcortical sensory aphasics whose deficit is at the level of single word comprehension, there may be no difference in the ability to repeat lists of words which are known, or lists of words whose meaning has been

'forgotten' as a consequence of disease (Warrington, 1975). In conduction aphasia an inability to repeat either polysyllabic words and/or lists of digits may be the only significant deficit, with other aspects of language functioning being relatively well preserved (Shallice and Butterworth, 1977). Impairment in the ability to repeat word lists and polysyllabic words does not invariably co-occur, and it has been argued that there are at least two identifiable subclasses of conduction aphasic (Shallice and Warrington, 1977). In those patients with difficulty in repeating polysyllabic words the deficit appears to be one at the level of speech production (Kinsbourne, 1972; Caplan *et al.*, 1986). In the other class of patient single word repetition is normal although 'span' for auditorily presented lists of verbal material is selectively impaired. This pattern of performance has been identified with an impairment in auditory verbal 'short-term memory' (Warrington and Shallice, 1969; Vallar and Baddeley, 1984).

In normal subjects the ability to repeat auditorily presented information verbatim is at the same time both strictly limited and highly variable. Thus the number of items which can be accurately repeated in a string of random numbers is a mere  $7 \pm 2$  items (Miller, 1956), with span for random word strings and nonwords being even less. In marked contrast the span for some types of sentence material may be as much as 30 items or more (*see* Baddeley, 1976). This variability in capacity has been attributed to information-loading factors such as transitional probabilities (Miller and Selfridge, 1950), formal syntactic constraints (Epstein, 1961), or to more complex interactions between syntactic and semantic processes (Jarvella, 1973). An assumption common to such theoretical accounts (which can be traced back to William James, 1890), is that of a single system underpinning or at least forming a central component of such repetition skills. The repetition of words, numbers and sentences has generally been thought to lie on a continuum of task difficulty which reflects the sensitivity of this unitary, if complex, system to different types of information load (e.g., Baddeley and Hitch, 1974; Hitch, 1980). Thus auditory-verbal information may be held in a passive phonological store which is maintained or refreshed by rehearsal processes (Baddeley, 1986).

However, the possibility that performance on all verbal repetition tasks does not invariably reflect the operation of a single system has recently been questioned (e.g., Wingfield and Butterworth, 1984) and multisystem models of short-term or working memory (anticipated in some respects by Craik and Lockhart, 1972) have been suggested. These postulate that temporary storage is not limited to any one coding format or level of representation (Monsell, 1984; Barnard, 1985). Indeed, Monsell has gone so far as to suggest that short-term memory may be a label for 'heterogeneous temporary storage capacities'. Such a viewpoint is consistent with the more flexible use of the labels 'short-term' or 'working memory' in the psycholinguistic literature which has, in general, avoided any commitment to the type(s) or level(s) of representation involved (e.g., Clark and Clark, 1977).

In the neuropsychological literature most investigations have assumed that a unitary system that mediates performance on auditory-verbal span tasks (e.g.,

Warrington and Shallice, 1969; Saffran and Marin, 1975; Allport, 1984; Vallar and Baddeley, 1984). In a previous study of speech production impairments in 2 conduction aphasic patients, we obtained the paradoxical result that they were able to repeat novel sentences better than familiar clichés (McCarthy and Warrington, 1984). This finding was doubly paradoxical in that the conduction aphasics' ability to repeat a novel sentence was remarkably well preserved despite their digit span being in the region of only one item. Indeed their repetition of sentence material was superior to that of a transcortical motor aphasic with a digit span of 4. (As an aside we note that profoundly amnesic subjects may perform normally on both types of task; *see* Zangwill, 1946; Talland, 1965.) This pointer towards a double dissociation between span and sentence repetition tasks alerted us to the possibility that there may be a discontinuity in the conduction aphasics span for word lists and for sentences; in brief, that there may be multiple short-term storage systems and that the processes underpinning these tasks may fractionate.

In this study we describe 2 aphasic patients whose span for auditory verbal lists was exceptionally poor; both patients had reliable recall for only one item. We report our investigations of their ability to repeat a wide range of verbal material and compare their performance with that of a transcortical sensory aphasic. This patient, whose single word comprehension was very impaired, had a span for lists which was within the normal range (reliable for 5 digits). Our 'span-impaired' patients' ability to repeat many types of sentence material verbatim was good but, in contrast, the sentence repetition of the 'span-preserved' case was remarkably poor. These findings indicate a double dissociation between the processes underlying word list and sentence repetition. We shall argue that these findings support models that postulate that there are multiple short-term memory systems and multiple levels of short-term memory representation.

## CASE REPORTS

### *Case 1*

R. A. N. was 55-year-old right-handed plumber. In January 1982, he sustained an intracerebral haematoma in the left parietal region for which he was treated conservatively (further details are given in McCarthy and Warrington, 1984). He was readmitted to the National Hospital in August 1985 in an attempt to improve management of his persisting focal epileptic attacks. On neurological examination the only finding of note was of a mild motor impairment affecting the right arm and leg. His most recent CT scan was unchanged from that of 1982 and showed a large area of low attenuation in the left parietal region consistent with an old infarction.

He was reassessed on the WAIS and obtained a Verbal IQ of 66 and a Performance IQ of 99. Individual subtest scores are given in Table 1. His recognition memory for nonverbal material was very satisfactory although his performance on a comparable recognition memory test for words was weak (*see* Table 1).

His spontaneous speech was fluent, with normal prosody and syntax. Although he used an appropriate vocabulary, there were frequent hesitations which appeared to be due to word-finding difficulties and very occasional phonemic paraphasic errors were also observed. His language skills were assessed in detail. On a test of phoneme perception using nonword stimuli he scored 68/72.



TABLE 1. WAIS, PEABODY AND MEMORY TEST SCORES\*

|                            | <i>Case 1</i> | <i>Case 2</i> | <i>Case 3</i> |
|----------------------------|---------------|---------------|---------------|
| Arithmetic                 | 0             | 4             | 9             |
| Similarities               | 4             | 5             | 0             |
| Digit span                 | 0             | 2             | 8             |
| Vocabulary                 | 7             | 8             | 4             |
| Picture completion         | 12            | 9             | 9             |
| Block design               | 9             | 8             | 18            |
| Picture arrangement        | 9             | 14            | 13            |
| Peabody picture vocabulary | 91            | 121           | NT            |
| Recognition memory         |               |               |               |
| Words                      | 5%            | 50%           | 25%           |
| Faces                      | 75%           | 50%           | 25%           |

\* Age-scaled WAIS scores, Peabody IQ equivalents (Dunn, 1959) and Memory (age-corrected percentile scores (Warrington, 1984)).

which is very satisfactory (McCarthy and Warrington, 1984). On the Oldfield and Wingfield (1965) picture naming test he scored 13/26 which indicates a moderate degree of naming difficulty. On a test of single word comprehension (Peabody Picture Vocabulary Test, Dunn, 1959) he obtained an IQ equivalent of 91. He had some difficulties on sections 5 and 6 of the Revised Token Test (De Renzi and Faglioni, 1978), scoring 22/36. A simplified version of this test (on which normal subjects score at ceiling) was constructed using a two-dimensional array (3 colours  $\times$  3 shapes). R. A. N. was asked either to 'show me' or 'hand me' one of the 9 stimulus items. He scored 33/72 correct. On the Parisi and Pizzamiglio sentence comprehension test (Lesser, 1974) his score was satisfactory (75/80).

His single word repetition was tested using the three syllable items from the word repetition test described in our previous study. His performance was considerably better than before in so far as he made no errors on the 30 high frequency words (more than 5 per million). He continued, however, to show some difficulty on the low frequency items, making phonemic paraphasic errors on 18/30 items. On sentence and cliché repetition his performance followed the same pattern as that reported previously: he scored 24/40 in the sentence condition and 14/40 in the repetition of familiar clichés (for further details, see McCarthy and Warrington, 1984).

His span for auditorily presented digits was assessed using 30 lists of 1, 2, and 3 items. The percentage of items correct is given in Table 2. In a further test of span for verbal material he scored 118/120 with visual presentation of three digit lists but only 31/120 with auditory presentation. Not only was his auditory span abnormally short but he also showed exceptionally rapid forgetting: he scored 18/20 in his immediate recall of a single letter, but following a mere 5 s distraction (number reading) his score dropped to 4/20. Auditory and visual evoked potential studies showed a comparable dissociation. In a Sternberg probe task there was no evidence of a normal P300 with auditory

TABLE 2. DIGIT SPAN: AUDITORY PRESENTATION OF 1, 2, AND 3 ITEM LISTS. PERCENTAGE OF ITEMS CORRECT FOR CASES 1 AND 2

|        | <i>List length</i> |          |          |
|--------|--------------------|----------|----------|
|        | <i>1</i>           | <i>2</i> | <i>3</i> |
| Case 1 | 100                | 65       | 51       |
| Case 2 | 90                 | 75       | 53       |

presentation. P300 was within the normal range in latency and amplitude following visual presentation of the same material (Starr and Barrett, 1987). Sixteen sentences of 3, 5, 7, and 9 words were generated using single syllable items from the high frequency bands of the Thorndike-Lorge count. Of these four sets of sentences he was able to repeat verbatim 75%, 75%, 63% and 25%, respectively. Considering R. A. N. has a reliable span for only one digit, his ability to repeat sentence material would appear to be remarkably good.

This case has both components of the conduction aphasic syndrome, namely a mild speech production deficit and a marked impairment on conventional tests of short-term memory with preserved sentence repetition occurring in the context of fluent spontaneous speech (Shallice and Warrington, 1977).

### *Case 2*

N. H. A. was a 42-year-old right-handed executive. He sustained a subarachnoid haemorrhage from a left middle cerebral aneurysm in June 1983. The aneurysm was clipped and, on recovery from the operative procedures, he had a right hemiplegia and was profoundly dysphasic. He made a slow recovery and at the time of the present testing the only neurological sign of note was a slight weakness of the right hand. He has been attending the National Hospital since November 1985 for speech therapy and for control of his persistent postoperative focal epilepsy.

He was tested on the WAIS and obtained a Verbal IQ of 65 and a Performance IQ of 104. The individual subtest scores are given in Table 1. His recognition memory for both visual and verbal material was very satisfactory (*see* Table 1).

His spontaneous speech, although hesitant, was syntactically correct with adequate phrase length, tonal variation and appropriate vocabulary. On a stringent naming test he scored in the average range, 15/30 (McKenna and Warrington, 1983). His performance on the Peabody Picture Vocabulary Test was excellent (IQ equivalent: 124). His performance on a shortened version of the Token Test was very poor indeed (3/15). Using a simplified version of this task with a two-dimensional array in which he had to 'hand me' or 'show me' 1 of a 9 item array (3 items  $\times$  3 colours), he scored 18/30 correct.

He was able to repeat polysyllabic words accurately, scoring 14/14 on high frequency and 12/14 on low frequency three syllable words from our (1984) repetition test. His digit span for auditory material was assessed using 10 lists of 1, 2, and 3 items. The percentage of items correct for each list length is given in Table 2. In a further test with visual presentation of 10 three-item lists he scored 80% correct. His immediate recall of a single auditory letter was satisfactory (19/20); there was, however, a marked decrement in his recall following 5 s of distraction (9/20). He was also tested on immediate verbatim recall of sentences using the sixteen 3, 5, 7, and 9 word items described above. On this task he scored 63%, 81%, 50%, 38%, respectively. In view of his exceptionally weak digit span, the performance of Case 2 in this test would appear to be remarkably well preserved.

This case has a striking deficit in conventional tests of short-term memory, one component of the conduction aphasia syndrome. His performance on tests of speech production were satisfactory. Other aspects of his language function, including his sentence repetition, were also relatively well preserved.

### *Case 3*

N. H. B. was a 62-year-old right-handed mechanic who complained of a progressive deterioration in his memory and language. He was referred to the National Hospitals in August 1985 for investigation of his difficulties. On examination there was no abnormality in the sensory or motor systems, digital subtraction angiography showed mild atheroma at the origin of the left internal carotid artery. His CT scan revealed a focal widening of the left temporal lobe sulci and dilatation of the left lateral ventricle. There were no other neurological signs of note other than the language difficulties which will be described below. No cause for his focal cerebral atrophy was found.

He was assessed on the WAIS and obtained a Verbal IQ of 71 and a Performance IQ of 118: his individual subtest scores are shown in Table 1. His exceptional difficulty on the subtest of vocabulary and his comparatively weak score on similarities appeared to be due to a comprehension deficit (e.g., when asked 'How are an axe and a saw alike?', he responded 'I can't remember what they are' and when asked to define 'Enormous' he responded 'I've forgotten'.) In contrast, his nonverbal reasoning skills were excellent and he scored at the 95th percentile on the Coloured Progressive Matrices. He scored at chance on a recognition memory test for words, and just within the average range on a memory test for faces (*see* Table 1).

His vocabulary was sparse, and the content of his conversation limited. He appeared to have marked word-finding difficulties but nevertheless his prosody and syntax were normal. On a test of phoneme perception he scored perfectly (72/72) and his repetition of both high and low frequency single three-syllable words was satisfactory (28/30 and 29/30, respectively). He named 9 items on the Oldfield and Wingfield naming test and failed to name any on the more stringent Graded Naming Test. He was also unable to name any items from their oral description.

His naming and comprehension difficulties were further investigated using 217 items from the Snodgrass and Vanderwart (1980) pool of words and pictures. He was asked either to define the spoken name of the picture or to identify the picture. His responses were rated as correct or incorrect by three independent judges using a lenient criterion requiring only that the core concept be conveyed. The percentage correct based on a consensus rating for three frequency bands for both auditory and visual presentation are given in Table 3. His performance on this task provides clear evidence of his auditory comprehension deficit; in addition there is evidence of a visual agnosia that is somewhat less severe than his auditory comprehension impairment. His deficit appeared to be stable over several testing sessions which we interpreted as suggesting that there was degradation of the semantic representations themselves, rather than an impairment of access to them.

His word span was investigated by assembling a pool of 24 one-syllable words, half of which were known to him and half of which were unknown to him (based on his performance on the Snodgrass and Vanderwart words and pictures). In terms of the number of items correct he scored 27/30 correct on both types of list; in terms of lists correct he scored 7/10 on the 'known' words and 9/10 on the unknown. By contrast his performance on a nonword span task using short monosyllabic items drawn from Glushko (1979) he scored 31/60 items correct and 2/20 lists correct. Thus although there is no difference in his span for known or unknown words he shows a normal decrement in his span for a novel vocabulary. (These findings replicate Warrington, 1975.)

His performance on repeating strings of digits was tested. With short lists his performance was error free (*see* Table 2) and it was further observed that he was able to repeat 4/5 strings of 5 digits and 3/5 strings of 6 digits correctly. In view of his relatively satisfactory digit span, his 'sentence span' was surprisingly weak: thus although his performance was error free in repeating our 16 3-

TABLE 3. IDENTIFICATION OF A PICTURE AND DEFINITION OF A SPOKEN WORD (CASE 3)\*

|                             | <i>Visual</i>   | <i>Auditory</i> |
|-----------------------------|-----------------|-----------------|
| High frequency<br>(50)      | 83<br>(n = 36)  | 61<br>(n = 36)  |
| Medium frequency<br>(25-50) | 82<br>(n = 28)  | 46<br>(n = 28)  |
| Low frequency<br>(25)       | 46<br>(n = 153) | 26<br>(n = 153) |

\* Percentage correct identification and definition of the Snodgrass and Vanderwart stimulus items.

word sentences, there was a significant error rate in repeating our 5, 7, and 9-word sentences (scoring 88%, 67%, and 25% correct, respectively). It is of some interest to note first, that he shows a clear-cut relationship between sentence length and probability of correct recall and secondly, that his overall level of performance is no better than that of cases with a digit span of only one item.

In summary, N. H. B.'s most striking deficit is a marked impairment of auditory comprehension which occurs in the context of intact single word repetition. We would classify Case 3 clinically as belonging to one subtype of the syndrome of transcortical sensory aphasia.

## EXPERIMENTAL INVESTIGATION

In this series of experiments we present evidence of our patients' ability to repeat word lists and sentence material verbatim. In each of the 5 experiments we compare the performance of the 2 conduction aphasic patients (the span-impaired cases) with that of the transcortical sensory aphasic (the span-preserved case). The stimuli were presented orally by one experimenter and recorded by the other, using broad phonemic transcription where appropriate. The patients' responses were also tape-recorded for further analysis. Word list stimuli were presented throughout using a 1 item per second rate, equal stress and pitch being given to each item (as in standard digit span tasks). The sentence material was read by the experimenter using a 'natural' pace and prosody. The patients were instructed to recall the test stimuli as accurately as possible. In each experiment a strict scoring criterion was adopted; however, the very occasional self-correction was accepted.

### *Experiment 1*

In the case reports, our two types of patient were classified as span-impaired or span-preserved on the basis of their ability to repeat lists of digits. In this first experiment our aim was to establish that this dissociation was also present for word list repetition. In addition, we manipulated the relative meaningfulness of the word list material, a variable that has previously been shown to be of significance for span-impaired patients (Warrington, 1982). This first experiment can be considered as a baseline for the subsequent experiments in which we contrast directly the patients' word and sentence repetition.

### *Procedure*

The procedure and stimulus material were adapted from that described previously by Warrington (1982). Three sets of 30 three-word lists were constructed consisting of verb, adjective and noun triplets (in this constant order). The three lists varied in their meaningfulness: in set A there was an arbitrary association between the verb, adjective and noun (e.g., walk, shiny, pools). In set B there was a loosely constrained relationship between the words (e.g., crawl, slow, baby) and in set C the triplet was more closely constrained (e.g., eat, green, apple). The material was presented using a Latin square to order conditions A, B, and C.

### *Results*

The percentage of items correct for each patient for each condition is given in Table 4. First, considering condition A (the arbitrary word combinations), the span-preserved case performed at a much superior level to the two span-impaired

TABLE 4. WORD TRIPLET REPETITION\*

|   |                                           | <i>Case 1</i> | <i>Case 2</i> | <i>Case 3</i> |
|---|-------------------------------------------|---------------|---------------|---------------|
| A | Random triplets                           | 44            | 39            | 81            |
| B | Meaningful triplets<br>(less constrained) | 66            | 80            | 76            |
| C | Meaningful triplets<br>(constrained)      | 79            | 87            | 73            |

\* Percentage of items correct.

cases, replicating the dissociation observed in digit span tasks. Secondly, considering the meaningfulness manipulation, increasing the meaningfulness of the triplet resulted in a clear and significant gain for the two span-impaired cases, but none whatsoever for the span-preserved case. Qualitatively it was observed that the errors made by the span-preserved case were phonemic (and frequently neologistic) paraphasias; they had many of the characteristics of 'Spoonerisms' with apparent migration of phonemes and syllables between items in the target string. Such errors were not observed in the span-impaired cases.

### *Comment*

In this experiment we have established first that the case whom we have designated 'span-preserved' on the basis of his ability to repeat strings of random digits also has a relatively well preserved span for words. Similarly, we have shown that the span-impaired cases were also equivalently impaired in their ability to repeat arbitrary word lists (condition A). Secondly, we have shown that the two types of case differ in their ability to benefit from the meaningfulness of the word list, with the span-impaired cases showing a significant gain when the association between words was less arbitrary. With regard to the span-preserved case his lack of sensitivity to the 'meaningfulness' manipulation complements the observation in the Case Report that there was no difference between words known and unknown to him in list repetition tasks.

### *Experiment 2*

The previous experiment has established that list meaningfulness is a significant variable in determining success or failure for the span-impaired subjects. In this experiment we wished to make a direct comparison between list and sentence repetition using matched vocabularies for the two tasks.

### *Method*

A set of 10 sentence frames were generated such that there were 2 vacant noun slots in each. The sentences were completed using 40 high frequency monosyllabic nouns, 20 of which were abstract, and 20 which were concrete (taken from the Brown and Ure, 1969, norms). These were placed in the sentence frames to make 20 matched sentences, 10 with an abstract word vocabulary and 10 with a

concrete word vocabulary (e.g., he took care with the law; he took salt with the meal). With one exception the sentence pairs were 6 words long, the exception being 7 words in length. Matched 3-word lists were derived from the sentences using the verb and the 2 nouns (e.g., took care law; took salt meal). These were presented in the same order in which they occurred in the sentences. Sentences and lists were given in an ABBA design (with 10 trials per block) to order conditions, the abstract and concrete vocabularies were alternated in presentation.

### Results

The patients' responses were scored in two ways (1) with respect to their performance on the critical word triplets and (2) with respect to their performance on each list or sentence considered as a unit. In the latter case a strict scoring criterion was adopted and verbatim repetition of the sentence or list was required. The percentage correct for each patient for each condition is given in Table 5.

Within-patient contrasts were computed for each measure using a binomial test. All comparisons were significant at less than the 5% level with the exception of Case 2 on the complete list vs complete sentence measure (*see* Table 5). Thus the span-preserved case was significantly worse at repeating whole sentences than in repeating word lists, whilst the converse trend was observed in the span-impaired cases. There was no difference between the concrete and abstract vocabulary for any patient in either the list or sentence conditions. The errors made by the span-impaired cases were minor paraphrases of the target in the sentence condition and order or omission errors in the list condition. The span-preserved case made numerous phonemic paraphasic errors; once again these had the characteristics of migration of phonemes within the spoken list or sentence.

TABLE 5. EXPERIMENT 2: REPETITION OF SENTENCES  
AND LISTS CONTAINING CONSTITUENT WORDS\*

|                       | <i>Case 1</i> | <i>Case 2</i> | <i>Case 3</i> |
|-----------------------|---------------|---------------|---------------|
| Complete sentence     | 55            | 60            | 30            |
| Complete list         | 15            | 40            | 75            |
| Key words in sentence | 88            | 90            | 63            |
| Key words in list     | 50            | 77            | 87            |

\* Percentage correct scored both for the total list/sentence and for 3 critical items per list/sentence;  $n = 20$  per cell.

### Comment

This experiment provides evidence for a double dissociation between list and sentence repetition. Considering first the span-impaired cases, the design of this experiment necessitated the use of word triplets with relatively high meaningfulness and high transitional probabilities; nevertheless, their performance was very poor in this condition particularly when compared with their ability to repeat the same material presented in a sentence context. Their verbatim recall of sentences, and indeed of the relevant key words in the sentence, was generally highly satisfactory, suggesting that the sentence advantage was not entirely due to a paraphrasing

strategy. Turning now to the span-preserved case, his pattern of performance was opposite to that obtained for the span-impaired cases; he was effectively hindered when recalling words placed in the context of a sentence despite showing a highly satisfactory ability to repeat the same material in the list conditions. The basis of the sentence context effect will be explored in greater detail in the following experiments.

### *Experiment 3*

In the Case Report on Case 3 we established that his ability to repeat words in a span task was not influenced by his ability to comprehend the same items; thus his span for 'known' and 'unknown' words was identical, and both were superior to his span for nonwords. In this experiment we wished to explore the effects of sentence context on his 'known' and 'unknown' word vocabulary using the span-impaired cases as controls for task difficulty.

#### *Method*

Two sets of 23 sentences were generated using a variety of simple syntactic constructions: 16 sentences were of 6 words, and 7 were 7 words long. One set of sentences contained one word which was 'unknown' to Case 3 (previously established by his failure both to define the word and to define a picture of the word using the Snodgrass and Vanderwart (1980) material; *see* Case Report). The other set of sentences contained one word which he had been able to comprehend on these same tests.

#### *Results*

The percentage correct for each patient in the 'known' and 'unknown' sentences is given in Table 6. There is a clear effect of sentence vocabulary for Case 3, but no effect for the span-impaired cases. This effectively eliminates task difficulty as an explanation for the performance of Case 3. There was a clear serial position effect for the span-preserved case which was mostly confined to the unknown vocabulary sentences (*see* fig. 1).

Qualitatively it was noted that the pattern of errors was very different for the span-impaired and the span-preserved patients. Whereas the span-impaired cases made occasional errors in verbatim recall, such as omission of an adjective or addition of an article, the span-preserved case made numerous phonemic errors.

TABLE 6. EXPERIMENT 3: REPETITION  
OF SENTENCES CONTAINING 'KNOWN'  
AND 'UNKNOWN' WORDS\*

|        | <i>'Known'</i> | <i>'Unknown'</i> |
|--------|----------------|------------------|
| Case 1 | 56             | 43               |
| Case 2 | 61             | 73               |
| Case 3 | 61             | 17               |

\* Percentage of each type of sentence totally correct.  
n = 23 per cell.

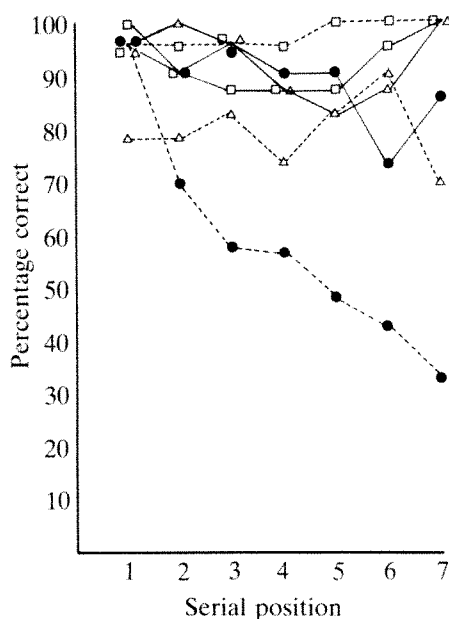


FIG. Repetition of sentences containing a 'known' and 'unknown' vocabulary. Percentage of words correct at each serial position for 6 and 7 word sentences.  $\Delta$  (Case 1);  $\square$  (Case 2);  $\bullet$  (Case 3); known (—); unknown (---).

These occurred in 14 of the 'unknown' sentences and in 4 of the sentences which contained a 'known' vocabulary. Migration of phonemes between words in the target frequently occurred in the responses of Case 3 (e.g., 'the flag was coloured bright red' → 'the blag was fullered with a right breg').

### Comment

In this experiment we have further evidence of a dissociation between sentence span and word span. Case 3 was able to repeat known and unknown words at an equivalent level in a list repetition task (*see Case Report*) and in this respect was similar to other cases with this type of transcortical sensory aphasia (Warrington, 1975). While vocabulary type had no effect on list repetition it had a strong effect on sentence repetition such that sentences containing unknown words presented a particular source of difficulty. The equivalent performances on the 'known' and 'unknown' vocabulary by the span-impaired cases indicates that there is unlikely to be a confounding effect of general task difficulty. The present findings indicate that verbatim sentence repetition is critically dependent on the ability to process the meaning of the constituent vocabulary whereas list repetition may be dependent upon presemantic lexical/phonological representations. The implications of these findings will be discussed below.



### *Experiment 4*

In this experiment we wished to explore the processes of sentence repetition in greater detail. In Experiment 3 we obtained evidence consistent with the view that the processes involved in sentence repetition were dependent upon the ability to comprehend the words within it. The question arises as to whether the effects were due to the patients' ability or inability to utilize passive semantic representations at the level of the single word or alternatively whether a more dynamic and integrative level of processing was implicated. If the representations involved were passive lexical ones then one would expect that partially incomplete sentences would be relatively easy for the span-impaired subjects, or at least they should not be more difficult than a complete sentence. On the other hand if the processes involve the operation of a more dynamic and integrative set of representations this condition would be expected to be particularly difficult for them.

#### *Method*

The stimulus materials were derived from the Bloom and Fischler (1980) sentence completion material. They consisted of two sets of 5 and 6-word sentences for which there are final word completion norms. The following conditions were tested (1) the sentence containing a high probability completion word (e.g., 'London is a very busy city'), (2) nonmeaningful sentence completion (e.g., 'London is a very busy river') and (3) a sentence fragment with the final word deleted (e.g., 'London is a very busy'). The 'incompleteness' of the sentence fragment was evident from the prosody used in the spoken presentation. In set A, 30 sentences were used with nonmeaningful and high probability completions having the same final word vocabulary attached to different contexts. This yielded 16 sentences in which part of speech was maintained but gross sectional restrictions violated, and 14 sentences in which both syntactic and semantic constraints were violated. In set B, 18 sentences were used. For these stimuli nonmeaningful completions were generated by choosing semantically related but contextually implausible completions (e.g., 'he caught the ball with his legs'). The two sets of sentences were presented (in separate sessions) using  $3 \times 3$  Latin squares to order conditions.

#### *Results*

The percentage correct for each patient for each condition for both sets of sentences is shown in Table 7. Considering first the patients' performance on the 'complete' and 'incomplete' sentences, summing across set A and set B there was a significant effect for Case 2 (Sign test,  $n = 21$ ,  $x = 5$ ,  $P = 0.03$ ), and a strong trend for Case 1 (Sign test,  $n = 19$ ,  $x = 5$ ,  $P = 0.06$ ). Overall there is a significant effect of sentence completeness for the span-impaired subjects: paradoxically this derives from their superior performance on the complete sentence condition. For the span-preserved case, there was no effect of sentence 'completeness'. Secondly, all 3 patients were sensitive to the sentence anomaly condition; this was marginally more pronounced for the set A sentences. Comparing across patients the only significant difference was that both Cases 1 and 2 were poorer on the 'incomplete' condition than Case 3 ( $\chi^2 = 5.6$  for Case 1,  $P < 0.02$ , and  $\chi^2 = 16.3$  for Case 2,  $P < 0.001$ , respectively).

Qualitatively the performance of the two types of patient was very different.

Case 2, the span-impaired patient whose performance on the incomplete sentences was particularly poor, made many completion errors in this condition when attempting to reproduce a sentence fragment (e.g., 'the thick mud stuck to her' → 'the thick mud stuck to her shoes'). Although Case 1 made some completion errors of this type, he also made errors of deletion (e.g., 'she was named after her' → 'she was named after'). Such patterns of response did not occur with complete sentences. By contrast, Case 3 never made a completion response in the 'incomplete' condition and, as in previous experiments, there was a tendency for serial position effects to occur in the complete sentence condition due to his omission of the latter part of the stimulus. Once again phonemic paraphasic migration errors were frequent in the responses of Case 3 and were very uncommon in the span-impaired patients.

TABLE 7. EXPERIMENT 4: REPETITION OF COMPLETE, INCOMPLETE AND ANOMALOUS SENTENCES\*

|                   |                             | <i>Case 1</i> | <i>Case 2</i> | <i>Case 3</i> |
|-------------------|-----------------------------|---------------|---------------|---------------|
| Set A<br>(n = 30) | Sentence<br>(whole)         | 43            | 47            | 40            |
|                   | Sentence<br>(incomplete)    | 20            | 17            | 47            |
|                   | Sentence<br>(anomalous end) | 7             | 23            | 6             |
| Set B<br>(n = 18) | Sentence<br>(whole)         | 56            | 39            | 33            |
|                   | Sentence<br>(incomplete)    | 33            | 0             | 50            |
|                   | Sentence<br>(anomalous end) | 28            | 17            | 28            |

\* Percentage of each type of 'sentence' totally correct.

### *Comment*

The main findings from this experiment were the differing effects of sentence 'incompleteness' for the span-impaired and span-preserved cases. The span-impaired cases found the incomplete sentence condition relatively difficult compared with the 'sensible' sentences whereas there was no differential effect for the span preserved case. Both types of patient showed sensitivity to the nonmeaningful condition. We would interpret these findings as being consistent with the position that sentence repetition skills are mediated by dynamic and anticipatory integrative processing. For the span-impaired cases this results in the paradox that making a sentence shorter by deletion of the final word makes it more difficult to repeat than the complete phrase. The theoretical implications of these findings will be discussed below.

### *Experiment 5*

In this experiment we evaluated the patients' ability both to comprehend and to repeat a list of words. We have already demonstrated that the 2 span-impaired

cases are poor at repeating short word lists, but that they are facilitated by increasing the 'meaningfulness' of the list (Experiment 1). In this experiment we investigated list meaningfulness, using a task in which we could establish the patients' ability to process the core concept conveyed by a list of words.

### *Method*

Fifty triplets of words were constructed such that they formed an abbreviated 'naming from description' task for which there was a high probability response, which could be used to establish comprehension (e.g., SMALL YELLOW BIRD). The stimuli were presented either for repetition, or as a naming from description task, using list intonation for presentation in both cases. In one condition the patients were required to repeat the list; in the other they were asked to name, or indicate by gesture that they had comprehended the implied question. The same triplets were tested in both conditions using an ABBA design. The full set of 50 stimuli were attempted by Cases 1 and 3, but due to experimental error a subset of 43 was presented to Case 2.

### *Results*

The percentage correct for each patient in the two conditions is given in Table 8. There was a highly significant effect of conditions for each patient. The effect was, however, in opposite directions for the span-impaired and the span-preserved cases. For the span-preserved case there was evidence of satisfactory list repetition, but not surprisingly his poor comprehension gave rise to many failures in the naming task, his commonest response being 'I don't know'. On further questioning there were only 2 further items on which adequate comprehension was indicated by gesture or circumlocution (scissors, saw). Some other responses gave evidence of partial comprehension of one or more elements of the triplet (e.g., NUMBER LEGS DUCK → four; BULL FIGHTING COUNTRY → war). In contrast the span-impaired cases gave prompt and appropriate answers in the naming condition; however they tended to incorporate a naming response into their attempt to repeat the triplet (e.g., COLOUR SUMMER SKY → summer blue sky; NUMBER LEGS HORSE → number horse four). In other instances the triplet was incomplete or misordered.

TABLE 8. EXPERIMENT 5: REPETITION AND COMPREHENSION OF WORD TRIPLETS\*

|                 | <i>Target<br/>response</i> | <i>Repetition</i> |
|-----------------|----------------------------|-------------------|
| Case 1 (n = 50) | 76                         | 26                |
| Case 2 (n = 43) | 91                         | 37                |
| Case 3 (n = 50) | 26                         | 68                |

\* Percentage of items correct.

### *Comment*

The most striking finding in this experiment was the difficulty which Cases 1 and 2 had in repeating highly meaningful triplets; that they were indeed highly meaningful for the patients is shown by their competent performance on the naming

task. It has previously been established that these span-impaired cases, in common with other similar patients reported in the literature, benefit from increasing the meaningfulness of the material to be repeated (Experiment 1). In the light of the previous findings we would suggest that their performance on the repetition condition was strikingly poor, indeed it was almost at the level of random word triplets. In contrast their ability to comprehend words presented as a list was surprisingly good, and far better than would be expected from their performance on other list or span tasks. We shall argue that this experiment provides further evidence for a dynamic and integrative memory system which is in some sense independent of that employed in list retention.

### DISCUSSION

In this series of experiments we have documented the repetition skills of two types of patient using a range of word list and sentence material. Two cases of conduction aphasia had markedly impaired ability to repeat or retain lists of numbers, letters and words, a pattern identified with a specific deficit in short-term memory (e.g., Shallice and Warrington, 1970). In the present context we have termed these cases as 'span-impaired' patients. The pattern of aphasia in Case 3 conformed closely to one subtype of the classical syndrome of transcortical sensory aphasia, that is, of a selective and frequency dependent degradation of verbal semantic knowledge (Warrington, 1975) in which word repetition and digit span are selectively preserved. This case we have designated 'span-preserved'.

The paradox that the span-impaired cases were able to repeat some sentence material at a better level than the span-preserved case was a surprising and hitherto undocumented pattern of results which raises a number of issues of theoretical interest.

Considering first the findings from the span-impaired subjects, despite having reliable digit spans of only one item, they were nevertheless frequently capable of repeating relatively long sentences absolutely verbatim even when the words contained in the sentence could not be recalled when presented as a list. In repeating word strings, they were facilitated by increasing list meaningfulness—but only up to a certain point. Thus they benefitted from decreasing the arbitrariness of a verb–adjective–noun combination. In contrast, on 3-word strings that contained an implicit question (e.g., small yellow bird) there was actually a decrement in their ability to repeat. Similarly, if the word string formed an incomplete sentence with a high probability completion, they had more difficulty with verbatim recall than with repetition of a whole sentence. In both experiments it was noted that they had marked difficulties in suppressing the 'answer' or the final word in their recall. In this respect they appear to be analogous to normal subjects when performing the 'Stroop' task, namely that the most automatic or available response was difficult to suppress. It should be noted that their introspections made it clear that this difficulty was not the product of any confusion with regard to the demands of the task.

Turning now to Case 3, in every experiment his performance contrasted with that of Cases 1 and 2. In brief, there was an absence of any effect of meaningfulness of word lists and there was a negative, rather than a positive, effect of sentence context in that he was able to repeat lists of words more adequately than sentences containing the same vocabulary. In sentences which contained only 1 word which we had established that he did not comprehend, his performance deteriorated markedly. There was no decrement in his sentence repetition when the final word was omitted and finally on the naming from description task his ability to repeat 3 words was significantly better than his ability to comprehend the question, the opposite result being obtained for Cases 1 and 2.

Qualitatively his performance had different characteristics from Cases 1 and 2. He made numerous phonemic paraphasic errors of a type which has not hitherto been described in the aphasia literature, namely of phoneme migration between words in the target. Phonemic errors were rare in the other 2 cases (despite the residual speech production deficit documented in Case 1), and on no occasion was phoneme migration observed. Case 3 showed a serial position effect in repeating sentences containing unknown words (*see* fig. 1), tending to omit the final words from the target. Serial position effects were not observed with the span-impaired patients. We would suggest that the memory system which the span-impaired cases were using for sentence repetition has all the characteristics of a dynamic, and integrative, language processor which operates in an anticipatory mode (e.g., Marslen-Wilson and Tyler, 1980). It would seem that this involves a short-term memory system which operates at a level of processing complexity which is beyond that of the single word. We would argue that we could account for certain findings from the span-preserved case in terms of an inability to use this system effectively. More specifically we suggest that his single word comprehension deficit underpins his difficulty with sentence repetition. Clearly a memory system which operates in a dynamic, and, more importantly, an anticipatory mode must have a high degree of lexical semantic knowledge available to it. If such knowledge is degraded or inaccessible, then it would be predicted that the operation of such a system would be severely compromised. In the extreme case, the patient's level of performance would be expected to be similar to that for random word lists. For our span-preserved case this interaction is most clearly demonstrated in the experiment in which his performance on repeating sentences containing a known and unknown word vocabulary was compared, the latter being particularly bad.

We have argued that there is a dynamic, integrative memory system that underpins sentence repetition which is selectively preserved in our span-impaired patients. If this is the case there must clearly be an alternative set of procedures mediating word list repetition: can we go any further and draw inferences with regard to the operation of this system on the basis of these experiments? The most direct evidence we have as to the properties and characteristics of this system comes from Case 3 where its operation can be observed in relative isolation (i.e., unconfounded by the involvement of lexical semantic knowledge). Case 3 was able to repeat both known

and unknown words at comparable levels in a span task, but had considerably greater difficulty in repetition of nonwords. This phenomenon has previously been reported and interpreted in terms of the operation of a presemantic level of processing which is sensitive to lexicality (Warrington, 1975).

We would wish to go further and suggest that Case 3 also sheds light on the code used by this system. On the evidence of the sensitivity of normal subjects to acoustic confusability, Baddeley (1966) argued that a phonemic code was employed in short-term memory for lists. The present evidence provides strong support for this position. Case 3 made numerous phonemic paraphasic errors, many of which reflected 'migration' of phonemes and phoneme clusters between items in the list. We would argue that Case 3, whose single word comprehension was very gravely impaired, responded in a manner which was qualitatively similar to normal subjects when attempting to repeat lists of nonwords (Ellis, 1980).

Turning to the issue of the roles of these memory systems in normal information processing, we have already suggested that this dynamic anticipatory memory system has many of the properties required for comprehension of normal conversation or running speech. However, it seems to be insufficient on its own for modulating such anticipatory processes in the face of anomalous, or low probability spoken input. Cases 1 and 2 appear to be unable to correct or modify the initial set of interpretative hypotheses upon which their recall of input is based. Consequently we would speculate that recourse to phonological storage is required in the monitoring and control of language processing when procedures based on anticipatory hypotheses are inadequate. In some respects phonological storage may be viewed as having the properties of a resource which can be used to refine and add precision to the operation of a more dynamic and forward looking language processor.

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## UNDERSTANDING: A FUNCTION OF SHORT-TERM MEMORY?

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### SUMMARY

We describe our investigations of the sentence comprehension abilities of 2 patients with a severe impairment in their auditory verbal short-term memory (conduction aphasia). Both were capable of comprehending a range of sentences, even when adequate comprehension was dependent upon the processing of order-dependent syntactic information rather than the utilization of semantic knowledge. Thus they performed satisfactorily on tests using plausibly reversible subject and object constituents with either active or passive verb phrases or prepositional phrases. Both, however, were impaired on sentences which departed from normal conversational conventions in terms of their reference to the order of event occurrence, or to the subject and object of an array. They were also very poor at performing comparative judgements, even when these involved a simple intrinsic attribute such as colour. These findings are discussed in terms of the role of auditory verbal short-term memory in backing up and backtracking over spoken information when conditions preclude the immediate understanding of auditory-verbal information.

### INTRODUCTION

Conduction aphasia is characterized by relative preservation of spontaneous speech and comprehension occurring in the context of a severe deficit in repetition. In a number of cases difficulty both in repeating, and in retaining, short lists of items has been attributed to an impairment of auditory verbal short-term memory. In such patients the immediate recall of spoken word, letter, or digit lists may be restricted to one item, and the ability to *retain* such information may be limited to a few seconds in the absence of continuous rehearsal (Warrington and Shallice, 1969; Warrington *et al.*, 1971; Saffran and Marin, 1975; Vallar and Baddeley, 1984a). It is thus a paradox that conduction aphasic patients may nevertheless be capable of repeating comparatively long sentences verbatim (McCarthy and Warrington, 1984).

In both the neuropsychological and psycholinguistic literature there has been considerable debate with regard to the functional role of the short-term memory system (e.g., Monsell, 1984). It is generally assumed that the memory system identified with list retention tasks does indeed have a role (other than the obvious

example of remembering telephone numbers). As it may be selectively impaired following a focal lesion to the brain, it appears likely that it may have developed or evolved in response to particular requirements of human information processing. A commonly held position is that this auditory verbal store provides a verbatim record which is necessary for some aspect(s) of language comprehension. In particular, it has been argued that such a record is required when comprehension is dependent upon the processing of word order and other syntactic information.

Evidence for this viewpoint may be drawn both from psycholinguistic studies of sentence processing in normal subjects, and from neuropsychological investigations of patients with selective impairment on digit and word span tasks (span-impaired patients). Studies of normal subjects' ability to recall sentences have indicated that verbatim content, including word order, and syntactic information, is generally lost following an intervening phrase, clause, or short delay (e.g., Sachs, 1967, 1974; Jarvella, 1970, 1971; Johnson-Laird and Stevenson, 1970). Such evidence has been accepted as indicating the involvement of auditory verbal short-term storage in the earlier stages of sentence processing (e.g., Clark and Clark, 1977). Neurological evidence from span-impaired patients is generally consistent with this inference despite there being some unexplained variability in performance between patients (E. Saffran, personal communication, 1985). Thus it has been found that sentences whose interpretation is syntactically but not semantically constrained may be poorly comprehended (Caramazza and Zurif, 1976; Caramazza *et al.*, 1981; Friedrich *et al.*, 1985; Vallar and Baddeley, 1984a).

Although there is wide agreement that auditory verbal short-term storage is involved in spoken language comprehension, there is no consensus with regard to the exact type(s) of processing for which this system is required. Nevertheless, despite this lack of precision, a very broad subdivision between the main perspectives can be drawn on the basis of their relative emphasis on the involvement of auditory verbal short-term storage in the contemporaneous or 'on-line' analysis of spoken language, namely that: (1) auditory verbal short-term storage is a crucial component of the on-line language processor and such a verbatim record may be of particular importance in parsing the spoken utterance prior to further linguistic analyses (e.g. Heilman and Scholes, 1976; Frazier and Fodor, 1978; Hitch, 1980; Marcus, 1980; Ellis and Beattie, 1986); (2) auditory verbal short-term storage is required as a back-up resource in those situations in which on-line processing is inadequate for comprehension. Under such conditions a verbatim record may be used to backtrack over spoken input and provide a basis upon which a sentence can be reanalysed for comprehension (e.g., Shallice and Warrington, 1970; Saffran and Marin, 1975; Baddeley, 1976; Caramazza and Zurif, 1976). These perspectives should probably not be viewed either as competing hypotheses or as complementary descriptions of a single flexible processing system. Current evidence indicates that they may refer to different levels or types of processing representation within a heterogeneous set of auditory verbal short term memory systems (e.g., Barnard, 1985).

Considering first the psycholinguistic evidence for such a fractionation, although the work of Marslen-Wilson and Tyler had documented the considerable sophistication of the on-line language processing system (Marslen-Wilson, 1975; Tyler and Marslen-Wilson, 1977; Marslen-Wilson and Tyler, 1980), evidence that this did not inevitably require the involvement of a passive phonological input buffer (e.g., Marshall, 1979) was first produced in the context of a verbatim recall task by Wingfield and Butterworth (1984). Their experiments suggested that running memory for sentences presented in normally spoken text was mediated by an anticipatory and dynamic short-term storage system which appeared to have somewhat different properties from that identified on the basis of performance on standard list memory tasks. Whereas the findings of Wingfield and Butterworth do not necessarily implicate dissociable short-term memories, and could conceivably reflect complex strategic interactions with a single level of representation, recent neuropsychological evidence is more conclusive.

In the accompanying study of 2 patients with grossly impaired spans for digits and words (reliable for one item), we observed relative preservation of sentence repetition (McCarthy and Warrington, 1987). Not only was sentence repetition relatively well preserved, but there was also evidence that it was mediated by anticipatory and dynamic on line processing at a level of analysis beyond that of the single word. For example, the patient's recall of complete sentences was superior to their recall of three words contained in the sentence. The opposite pattern was observed in a span-preserved case with degraded semantic knowledge and preserved span.

Having shown that the systems which mediate list retention and on-line language processing may be doubly dissociated, the question remains as to how the passive phonological storage system might be involved in language processing. If the hypothesis is adopted that it operates as a back-up store when on-line processing fails, then it is necessary to specify the conditions under which such failure might occur. For example, if the on-line processing system has limited syntactic competence, then it would be expected that backtracking operations might be required routinely in order to disambiguate plausibly reversible constituents. Span-impaired patients, in whom the relative integrity of on-line processing has been demonstrated, provide a unique opportunity for evaluating both the range of linguistic procedures available to the on-line system and also for exploring the role of auditory verbal short-term storage in language comprehension.

In this series of experiments we report our further investigations of the sentence comprehension abilities of the 2 span-impaired conduction aphasic patients described in the accompanying paper. In this report we shall describe a series of experiments which demonstrate that despite having reliable digit spans of only one item, they were nevertheless capable of comprehending a variety of order dependent sentence constructions. At the same time, on tasks in which order was irrelevant, their comprehension of verbal information was clearly impaired. We shall discuss

these findings in terms of the utilization of auditory verbal short-term storage in backing up and backtracking during the 'understanding' of running speech.

## CASE REPORTS

The 2 patients with conduction aphasia who participated in this study have been described in detail in the accompanying paper (McCarthy and Warrington, 1987). The main clinical information is summarized below.

### *Case 1*

R.A.N. was a 54-year-old right handed plumber who sustained an intracerebral haematoma in the parietal region of the left hemisphere for which he was treated conservatively. He had mild speech production difficulties and was severely impaired on conventional tests of auditory-verbal short-term memory, the two components of a conduction aphasia. Otherwise his language skills were relatively well preserved.

### *Case 2*

N.H.A. was a 42-year-old right-handed executive who sustained a subarachnoid haemorrhage from a left middle cerebral aneurysm in 1983. The aneurysm was clipped. His major residual deficit was a severe impairment in conventional tests of auditory-verbal short-term memory. Other aspects of his language skills, apart from some hesitancy in his spontaneous speech, were relatively well preserved.

## EXPERIMENTAL INVESTIGATION

### *Experiment 1*

In this experiment we investigate the patients' ability to comprehend sentences in which word order is critical.

### *Method*

The material was an expanded version of that described by Schwartz *et al.* (1980) (made available to us by E. Saffran). The task requires the subject to match a sentence spoken by the examiner to one of a pair of pictures: each picture of a pair shows the same two characters engaged in a plausibly reversible transitive action (e.g., waving, applauding, painting, etc.) The task is structured so that failure to maintain noun or pronoun order around a verb results in a mismatch, the agent or subject in one picture being the recipient or object in the other picture (and vice versa). The sentences and pictures have been constructed so that pragmatic biases are minimized, for example, (1) The dancer applauds the clown, (2) The clown is applauded by the dancer. The test uses an equal number of active and passive constructions, and comprises 78 sentence-picture items.

### *Results*

Case 1 scored 65/78 on this task (5 errors on the active voice sentences and 8 on the passive). Case 2 scored 73/78 correct.

### *Comment*

Case 1's performance, although somewhat weaker than normal, is creditable considering his very severe impairment in retaining word or digit lists. More impressive was the performance of Case 2 whose error rate was minimal. Overall, these findings suggest that the form of short-term memory which is implicated in span tasks is not *necessarily* required for the comprehension of sentences in which word order is critical.

### *Experiment 2*

In this experiment we wished to investigate the relative contributions of syntactic and conceptual complexity in processing longer order-dependent sentences using the adverbs 'before' and 'after'. The techniques and methodology were adapted from those which have been described in many studies of language comprehension in young children (e.g., Clark, 1971; Johnson, 1975; Slobin, 1982). Two variables were manipulated, first, the position of the adverb in the sentence and secondly the order of events referred to by the sentence. The constructions (1) *She watered the flowers before she went to the shops*, and (2) *She went to the shops after she watered the flowers*, are syntactically simple in that the main clause precedes the subordinate clause. This is not the case for (3) *Before she went to the shops she watered the flowers*, or (4) *After she watered the flowers she went to the shops*, in which the subordinate clause precedes the main clause. The sentence types also differ in their conceptual complexity, sentences (1) and (4) referring to events in an order which matches their temporal order of occurrence whereas this is reversed in sentences (2) and (3). Up to the age of 5 years (approx.), children make errors on this latter type of sentence which violates normal conventional usage (the 'order of mention contract'; Clark and Clark, 1977).

### *Method*

Five pairs of pictures were prepared which showed the same individual engaged in two different actions (e.g., a woman watering flowers, and the same woman at a supermarket). The subject was required to position the pair of pictures from left to right on the desk to indicate the order of occurrence of events in a spoken sentence. Forty sentences describing the pictured actions were constructed, and these were joined into a single sentence using the adverbs 'before' and 'after' as in the examples given above.

For half the sentences events were referred to as occurring in one order; this was reversed for the remainder. The sentence types were presented in a pseudorandom order, the different picture pairs in a constant order. The sentences were spoken using a 'natural' pace and prosody, and the patient was then given the pair of pictures to place in the appropriate left to right sequence (Case 2 was not available for this experiment).

### *Results*

Case 1 scored 37/40 correct on the sentences which maintained the conventional order of mention and only 26/40 correct on those that reversed the order of event occurrence. There was no effect of syntactic complexity in that the position of the main clause in the sentence did not affect his performance.

*Comment*

The pattern of task difficulty in this experiment does not suggest that Case 1 is impaired in syntactic processing per se, but rather that he is affected by the conceptual complexity of the task. He was clearly biased towards interpreting sentences in terms of conventional order of mention. This could have arisen for two reasons: first, it is possible that he attempted to solve the task by simply processing the first event referred to by the experimenter and ignoring the second half of the sentence or, secondly, these findings may indicate that his apparent difficulties in sentence processing are due to the additional cognitive operations which are necessary when conventional conversational 'rules' are contravened. The first possibility seems a priori unlikely since a strategy of this type would be expected to yield below chance levels of performance on the sentences in which order of mention was reversed; however, it cannot be entirely ruled out as a contributing source of bias in this particular experiment. The following experiment was designed to investigate the possible role of conventional conversational usage in sentence comprehension using a technique which was not open to this possible source of bias.

*Experiment 3*

In this experiment we explored a different aspect of the relationships between order-dependent processing, conversational conventions and real world knowledge, using a technique adapted from Huttenlocher and her colleagues (*see* Huttenlocher *et al.*, 1968). This technique enables the experimenter to vary the 'real world' salience of items which are referred to by the subject and object constituents in a prepositional phrase. Thus in the phrase 'a is above b', a is the logical subject of the statement (the thing that is being above) and b is the logical object (the thing that a is being above). Given two moveable tokens, and asked to place one above the other, children and adults tend to initiate action using the sentence subject. If one of the tokens is fixed in position, the sentence can be comprehended easily if the fixed token is the object of the sentence. If, however, the fixed token is referred to in subject position, then the sentence becomes less easy to comprehend. Huttenlocher *et al.* suggested that in this situation comprehension required an additional mental transformation of the examiner's statement so that the mobile token became the logical actor referred to by the statement. Thus given a mobile green block and a fixed red block and the statement 'the red block is on top of the green block', some children said 'Oh you mean the green block goes under the red one'.

Since the preceding experiment suggested that Case 1 had particular difficulties when departure from conversational conventions resulted in a linguistically simple, but cognitively complex statement, it would be predicted that this latter condition would be considerably more difficult for span-impaired patients than conditions in which the sentence subject/object relations corresponded to those implied by the visual array. An additional interest of this experiment was to investigate the role

TABLE 1. HUTTENLOCHER'S COMPREHENSION TASK\*

|               | Case |     |
|---------------|------|-----|
|               | 1    | 2   |
| Subject fixed | 53%  | 59% |
| Object fixed  | 84%  | 78% |
| Neither fixed | 89%  | 83% |

\* % correct. n = 64.

of the relative 'abstractness' of the sentence instructions by using colour terms (rather than concrete nouns) in subject and object positions.

### Method

The procedure was a modified version of the task described by Huttenlocher *et al.* (1968). Two sets of locative expressions were investigated (1) above and below and (2) in front of/behind. The subject was asked to place small models of a man (wearing black) and a woman (wearing red) on the desk in accordance with a spoken instruction. For condition (1) a three-step 'staircase' was constructed on which the models could be placed. Three arrangements of the arrays were used, in one both models were moveable, and in the other arrangement either the model man, or the model woman was fixed in position. In the concrete condition the patients were asked to 'place the man/woman above or below the woman/man'; all permutations were tested equally often. Similarly, when testing 'in front/behind' all permutations of the instruction to 'place the man/woman in front of or behind the woman/man' were tested in both the moveable and the fixed conditions. For the more abstract, colour name condition, the terms black/red were substituted for man/woman. Moveable and fixed conditions were ordered in an ABBA design using 8 trials per block and locative types were presented in blocks of 32 trials. Abstract and concrete conditions were alternated.

### Results

The percentage correct for each patient for each condition is given in Table 1. Since there was no overall effect of 'abstractness', the data were combined across this variable in analysis. There was a significant effect of conditions  $\chi^2$  (d.f.2) = 17.3,  $P < 0.001$ , for Case 1 and  $\chi^2$  (d.f.2) = 6.3,  $P < 0.05$  for Case 2. Both patients were consistently poor on the condition in which conventional conversational usage was violated, indeed their scores were not reliably above chance on this condition. In contrast when conventional subject-object usage was maintained there was evidence of satisfactory ability to process the same order dependent sentences.

### Comment

Although both patients are capable of comprehending reversible locative expressions, their comprehension is affected by the situation in which such comprehension must be demonstrated. When the conventional form of reference to subject and object in the prepositional expression was not adhered to, then the patients were impaired. Huttenlocher has argued that under such conditions an additional cognitive operation is necessary for successful comprehension, namely that difficulty in performing this task is not due to the demands of linguistic processing per se, but rather to the requirement to perform additional restructuring

operations on such linguistic information. Thus the initial mapping of constituents onto subject and object constituents of a propositional (or higher level) representation may be conducted on-line, the subsequent revision, and modification of this representation so that it is compatible with other evidence from the context (required in this instance by the subject/object roles of the tokens in the display) may require the use of back-up, and backtracking, resources.

#### *Experiment 4*

In this experiment we explored the hypothesis that the patients' impairments were independent of any form of order processing but, instead, that they were attributable to the requirement to use spoken information in additional constructive and reconstructive operations. An adequate test of such a hypothesis requires an elementary task which cannot be solved directly on the basis of a propositional representation constructed on-line, and for which a veridical representation of the spoken information is therefore required. Simple comparative judgements would appear to meet these requirements in that they place a significant load on the construction and reconstruction of novel cognitive representations, and a minimal load on other aspects of processing. This applies whether the comparison is based on a relatively intrinsic feature such as colour, or a more arbitrary task-dependent feature such as size. Both intrinsic and arbitrary comparisons were evaluated in this experiment.

#### *Method*

A set of 5 pairs of words referring to items varying in colour and size were assembled (e.g., poppy, lettuce). These were placed in question frames, requiring a comparison either in terms of colour or size. The same item pairs were used in both types of comparison. The questions were framed so that maintenance of noun order was irrelevant (e.g., Which is red, a poppy or a lettuce?). The order of items was combined factorially so that the same items appeared in the initial position of half the sentences and in the final position for the remainder. This yielded a  $2(\text{colour}) \times 2(\text{size}) \times 2(\text{order})$  set of comparisons for each pair of items, and 40 trials for the block. A second set of items was constructed from 5 pairs of animal names which could be contrasted either in terms of the intrinsic attribute 'dangerous/tame' or in terms of size. As in the first part of the experiment the names were placed in a non order-dependent sentence frame for the comparison task (e.g., Which is more dangerous, a scorpion or a lamb?'. Which is larger, a scorpion or a lamb?). The same item pairs were used in each comparison type. The factorial combination of dangerous/tame by size and by order gave a 40 trial set of comparisons also for this block.

In both blocks, items in the more 'arbitrary' size comparison were selected on the basis of pilot investigations so that they were not in some sense 'marked' as large or small, (e.g., elephant, mouse) but rather so that they were (as far as possible) unambiguously larger or smaller than the other item in the comparison pair. The comparison questions were presented in two sets of 20 trials per block and the colour/size comparison items were presented before the tameness/size comparisons. The extrinsic and intrinsic comparison types were randomized within blocks.

#### *Results*

The percentage correct for each patient for the intrinsic and extrinsic conditions (summing across comparison types) is shown in Table 2. There was no significant



TABLE 2. SIMPLE COMPARATIVE JUDGEMENTS\*

|                      | <i>Case</i> |          |
|----------------------|-------------|----------|
|                      | <i>1</i>    | <i>2</i> |
| Intrinsic attributes | 75%         | 53%      |
| Size                 | 73%         | 44%      |

\* % correct. n = 40.

difference between the patients' ability to perform intrinsic, or extrinsic comparisons. We wish to emphasize the marked impairments which both patients show in performing the exceptionally simple intrinsic comparison task (one which is comfortably within the range of 3-year-old children). Qualitatively it was observed that the patients were slow and laboured in their performance, and claimed that they had marked difficulty in retaining the questions which they were asked. A number of their errors were intrusions from previous comparison questions within the same block of trials, (e.g., Which is green, a fox or a gooseberry?→poppy). Case 2 attempted a variety of strategies for coping with the questions including using his hands as a means of retaining the comparative adjective.

### *Comment*

The present findings support the hypothesis that the patients' difficulties are attributable to the requirement to use linguistic information in a supplementary set of cognitive operations. They cannot in any way be attributed to an impairment in the processing of syntactic information since this was of limited relevance in this task. Indeed for Case 2 there appears to be a clear dissociation between his good ability to process order-dependent sentences, and his inability to perform a cognitive operation on the basis of nonredundant spoken information. There is also no question that this difficulty with comparative judgements reflected a failure to comprehend the individual word: Case 1 has an average, and Case 2 a superior, receptive vocabulary (Peabody Picture Vocabulary).

## DISCUSSION

In this series of experiments we have documented the sentence comprehension skills of 2 conduction aphasics who had profound impairments in the retention of spoken lists of random numbers, letters, and words. Despite having reliable digit and word spans of only one item, there was evidence that both Cases 1 and 2 were capable of comprehending a variety of sentence types and, in particular, there was no evidence of specific comprehension difficulties on sentences whose interpretation was dependent on syntactic rather than semantic information. Thus they were able to perform satisfactorily on a test of sentence comprehension in which noun phrases were plausibly reversible around either an active, or passive verb phrase

(Experiment 1). With longer reversible sentences, using the constructions 'before' and 'after', there was also evidence of adequate processing of syntax. Similar good levels of comprehension were documented using reversible locative constructions (e.g., 'above', 'below'). However, the patients had specific difficulties when normal conversational conventions were contravened (Experiments 2, 3) and when the verbal information had to be used in a subsequent set of cognitive operations (Experiment 4).

Our aim in this investigation has been to delineate the conditions under which comprehension impairments can be identified in span-impaired patients with conduction aphasia. We would argue that the present findings, together with those of the accompanying paper, are consistent with the view that both of the present cases have relatively intact on-line language comprehension skills, but that they are impaired in those operations which require backtracking over spoken input. Specifically we suggest that the short-term memory system which subserves list retention has the function of a back-up resource for noncontemporaneous or 'off-line' language processing. Thus this system may be used when the individual needs to 'replay' spoken input in order to make a supplementary or subsequent attempt at comprehension.

The hypothesis that auditory verbal short-term memory might function as a back-up resource is not novel, and there have been a number of hypotheses with regard to the situations in which its use might be required. Thus it has been suggested that it might be useful when the initial interpretation of a sentence is in error (Garrett, 1970; Saffran and Marin, 1975; E. Saffran, personal communication, 1985) and/or when on-line processing is inadequate for comprehension of spoken input (Shallice and Warrington, 1970; Baddeley, 1976; Vallar and Baddeley, 1984*a, b*; E. Saffran, personal communication, 1985).

We wish to develop these earlier suggestions and on the basis of the present evidence to argue that the utilization of auditory verbal short-term storage is required for backtracking when an appropriate central cognitive representation cannot be constructed on-line. By the term central cognitive representation we wish to refer to a level of processing which is not only based on analysis of the spoken utterance but is also one which incorporates the real world knowledge and expectancies which underpin understanding (*see* Webber, 1981; Garnham, 1985; Johnson-Laird, 1983). It can be considered as a level of representation in which there is an interaction between a spoken phrase and other salient sources of evidence such as preceding or anticipated speech, events, or other contextual information. Specifically we wish to argue that backtracking resources are likely to be required under those circumstances in which the results of processing auditory verbal information cannot be immediately transcoded into such central cognitive representation.

On the basis of the present evidence we would suggest that the following three conditions are likely to impose constraints upon such transcoding operations and therefore on the requirements to resort to backtracking operations: (1) the rate of

information presentation and the latency with which a sufficiently unambiguous central cognitive representation can be constructed; (2) the importance of extralinguistic assumptions with regard to interpretation of the spoken message and their relationship to the central cognitive representation; and (3) when the achievement of a central cognitive representation requires supplementary cognitive operations to be performed on the spoken input. These three limitations are unlikely to be mutually independent, and they are merely highlighted in this context as characteristic of those situations in which backtracking operations appear to be necessary so that a spoken message can be understood. We shall now consider each of these conditions in greater detail in relation to our experimental evidence.

First, both patients, in common with previously documented span-impaired cases, show a dramatic dissociation between their normal levels of performance in comprehending and naming items presented in spoken descriptions (e.g., What is the name of the thin grey dust that remains after something has burned, such as a cigarette?) and their inability to perform token test (type) instructions (e.g., Put the red circle on the blue triangle). That this cannot be attributed to a primary syntactic impairment (as argued by Caramazza and Zurif, 1976) was shown in the accompanying paper by both patients' extremely poor performance on a simplified version of the task in which syntactic demands were minimized, and word order was irrelevant (e.g., Pick up red circle). The patients' difficulty on token test type instructions appears to be due in part to the temporal constraints involved in setting up an appropriate central cognitive representation, the rate at which such propositionally abstract spoken information is presented being incompatible with the latency requirements of constructing a detailed central representation.

Secondly, both patients were sensitive to the effects of extralinguistic assumptions and contextual information on an adapted version of the Huttenlocher locative comprehension task. When the 'fixed' or logical object element in the task array was referred to in the subject position of a sentence, they had significant difficulties with the task. For example if asked to place tokens so that a mobile red piece was behind a fixed black token, then the patients' performance was satisfactory; however, if asked to carry out the same instruction (i.e., 'red behind black') with a fixed red token then their performance was impaired. The patients' deficit, therefore, was not at the level of syntactic processing but rather at the stage of matching the spoken sentence to the visual array. They were specifically impaired under conditions in which there was conflicting linguistic and 'real world' non-linguistic (pragmatic) evidence with regard to the subject and object roles of the tokens. Analogously, Case 1 was sensitive to the order of mention in the adverbial before/after sentences, and had considerable difficulty in showing understanding of the sentences in which normal conversational conventions were violated by describing events in the reverse order of their occurrence. In this situation there is a clear conflict between expectancies based on real world experience and the order of occurrence expressed in the test sentences.

Thirdly, both patients were significantly impaired in performing very easy com-

parative judgements, (e.g., Which is red, a poppy or a lettuce?). Such a task places a minimal load on sentence comprehension, but maximizes the requirements to construct, retain and contrast central cognitive representations. The result of sentence processing must therefore be used in a secondary or supplementary set of cognitive operations in order to develop an adequate and appropriate central model. Accurate performance of the comparison procedure requires access to a veridical verbatim record of the spoken sentence.

In summary, we would argue that the on-line language processing system which is preserved in these patients has the capacity to perform a range of linguistic operations, including syntactic processing. When additional operations are necessary in order to transcode between the auditory-verbal message and a developing central cognitive representation, then this backtracking facility may be used. Auditory verbal short-term storage provides a veridical record of the spoken information which can be 'replayed' when the central cognitive representation cannot be constructed on-line.

The processes involved in understanding a sentence, rather than in merely comprehending it, appear to reflect an interaction between linguistic and non-linguistic or pragmatic levels of representation. As with other cognitive skills, sentence comprehension would appear to be a complex and multifaceted process, the various subcomponents of which can potentially break down highly selectively in a variety of aphasic syndromes.

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# THE ROLE OF NMR IMAGING IN THE ASSESSMENT OF MULTIPLE SCLEROSIS AND ISOLATED NEUROLOGICAL LESIONS

## A QUANTITATIVE STUDY

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### SUMMARY

The form and distribution of MRI abnormalities in 114 patients with clinically definite multiple sclerosis (MS) have been compared with observations on 53 apparently healthy individuals, 129 patients with isolated focal neurological lesions with which MS often presents (51 patients with optic neuritis, 44 with isolated brainstem lesions and 34 with isolated spinal cord syndromes) and 105 patients with disorders which may be confused clinically or radiologically with MS. The latter comprised 55 patients with cerebral vascular disease (including 7 cases of dementia with diffuse white matter disease), 24 with degenerative ataxic disorders, 8 with cerebellar tonsillar ectopia, 7 with sarcoidosis and 11 with a variety of other disorders.

Periventricular abnormalities were found in all but 2 patients with MS and discrete white matter lesions in all but 12. Characteristically the periventricular changes in MS were irregular in outline. Periventricular abnormalities which were often milder and of smooth outline were seen in 37/55 patients with cerebral vascular disease, 9/24 with cerebellar degeneration, 5/7 with sarcoidosis and in 2/3 apparently healthy individuals over the age of 60. The appearances in the 7 cases of dementia resembled those with advanced MS.

Cerebellar and/or brainstem atrophy characteristic of the cerebellar degenerations, in the absence of white matter abnormalities, was helpful in making the distinction from MS. Congenital anomalies and tumours in the region of the brainstem and foramen magnum were readily shown.

More than half the patients with symptoms attributable to isolated focal neurological lesions had additional lesions at presentation. MS cannot be diagnosed in these cases at presentation, but repeat scans after 5 to 20 months in 25 patients with optic neuritis and 10 with clinically isolated brainstem lesions have shown new lesions in 7 (20%). The patients with new lesions fulfil the criteria for clinically probable MS (Poser *et al.*, 1983).

Measurements of  $T_1$  and  $T_2$  in vivo permitted the distinction of acute from chronic brainstem lesions. There were quantitative differences in  $T_1$  and  $T_2$  between the normal appearing white matter

in MS and normal brain. Studies of postmortem brains provided convincing evidence that the MRI abnormalities in MS correspond with plaques. Evidence is adduced to support the view that an important source of the abnormal NMR signals in acute lesions is oedema, and in chronic lesions is gliosis; demyelination per se is unlikely to make an important contribution.

## INTRODUCTION

The demonstration by Young *et al.* (1981) that nuclear magnetic resonance (NMR) imaging (MRI) is very sensitive in detecting lesions in patients with multiple sclerosis (MS) has had a major impact on the way in which patients suspected of having the disease are assessed. The original observations have been widely confirmed and it is clear that MRI is superior to other imaging techniques in demonstrating abnormalities (Young *et al.*, 1981; Lukes *et al.*, 1983; Runge *et al.*, 1984; Ormerod *et al.*, 1986a). In defining the clinical role of MRI, several questions need to be answered. What is the form and distribution of the abnormalities in MS? Are they specific? What do the abnormalities represent pathologically? What can MRI tell us about patients presenting with symptoms attributable to isolated focal lesions of the type seen in MS (hereafter referred to as isolated lesions)? What is the sensitivity of MRI relative to evoked potential methods in detecting lesions in various parts of the central nervous system?

We have addressed these questions by systematically investigating 401 individuals of whom 53 were healthy controls, 114 had clinically definite MS, 129 had isolated lesions of the kind with which MS can present (optic neuritis, brainstem or spinal cord syndromes), and 105 had a variety of conditions which may be confused clinically or radiologically with MS, including cerebral vascular disease (inflammatory and noninflammatory), intracranial sarcoidosis, cerebellar degeneration and congenital anomalies and tumours in the region of the foramen magnum, brainstem and spinal cord. Some aspects of this work based on smaller numbers of cases have been reported previously (Ormerod *et al.*, 1984; Ormerod *et al.*, 1986a, b, c). In this paper we review our experience of MS and the various control groups, and present serial observations on patients with isolated lesions; in addition we describe the results of an investigation of the relationship between images of postmortem brain and the form and distribution of the lesions in MS.

## METHODS

### *Imager*

The NMR imager in this study was a 0.5 Tesla Picker superconducting system which was used to form proton NMR images. A few observations were performed at a lower field (0.25 Tesla). The sequences and methods described pertain to the higher field. Following upgrade to 0.5 Tesla a number of further alterations in hardware and software resulted in a progressive improvement in image quality. These include enhanced performance in radiofrequency (RF) transmitter, frequency synthesizer (for generation of RF pulse), gradient coils, and surface receiver coils.

Brain images were all obtained using the standard head receiver coil as supplied by the manufacturer. For imaging of the optic nerve and spinal cord, closely applied surface coils were used (Axel,



1984; Bydder *et al.*, 1985a). These coils were initially made by one of the authors (G. J.) and later supplemented by others made by the manufacturer. Surface coils give improved signal-to-noise ratio and hence permit improved spatial resolution images of specified local areas.

### Sequences

We aimed to image as much of the brain as possible and to identify the maximum number of lesions. Multislice imaging protocols making images in the axial (transverse) plane were employed. In this way either 8 or 16 slices of 10 mm thickness and 2 mm interslice separation were examined. Later software improvements allowed the use of contiguous 10 and 5 mm slices. For imaging the spinal cord and optic nerve 5 mm slices were used either as single slice imaging or as part of the multislice protocol.

An imaging matrix of  $128 \times 256$  was routinely employed, giving pixel dimensions of approximately  $2.4 \text{ mm} \times 1.2 \text{ mm}$ . For some studies, particularly of the spinal cord and optic nerve, a higher resolution ( $256 \times 256$ ) matrix was used, resulting in a pixel size of  $1.2 \text{ mm} \times 1.2 \text{ mm}$ . Each line of data collection was subject to 2 averages.

For head imaging, spin-echo (SE) and inversion-recovery (IR) sequences were used. The nomenclature for SE and IR scans are  $\text{SE}_{\text{TR}/\text{TE}}$  and  $\text{IR}_{\text{TR}/\text{T}_1/\text{TE}}$ , respectively, where the repetition time  $T_R$ , the inversion time  $T_I$ , and the echo time  $T_E$ , are defined as in the glossary of NMR terms of the American College of Radiologists (American College of Radiology, Subcommittee on NMR Nomenclature and Phantom Development, 1984). On the SE sequences, lesions appear as areas of increased signal (white) relative to the underlying brain. As many of the lesions were periventricular in site their detection was facilitated by employing sequences whose imaging parameters were such that the lesions were of the highest signal and white matter was of higher signal than CSF. As the echo time of the sequence is increased the CSF tends to change from being of low signal (black) to higher signal (white), thereby potentially obscuring the periventricular lesions. Although these longer echo sequences were often less useful for identifying periventricular lesions, they sometimes enabled discrete lesions within the cerebral white matter to be visualized more easily.

With inversion-recovery sequences (apart from Short  $T_I$  Inversion Recovery (STIR) sequences, *see* below) the lesions appear of lower signal than brain (black), as does CSF. As a result, small periventricular lesions may be undetected and simply mistaken for partial volume artefacts around the margins of the ventricles.

No single sequence was optimal for demonstrating all the lesions (*see* fig. 1); this has also been the experience of other groups (Runge *et al.*, 1984), and probably reflects differences in the water content (water proton density) and relaxation time (*see* Discussion) of the lesions. The use of more than one sequence, with differing dependence on  $T_1$  and  $T_2$  for the generation of contrast, allows the maximum number of lesions to be detected when multislice imaging is used with each of the sequences.

Optic nerve images were obtained using the modified IR sequence STIR (Bydder *et al.*, 1985b) in which the signal from orbital fat is suppressed but the contrast between lesions and the surrounding optic nerve is enhanced.

For the spinal cord a variety of sequences was used. For demonstrating anatomical relationships, cord size and shape and structural abnormalities in the region of the foramen magnum, an  $\text{SE}_{500/40}$  sequence was employed. For demonstrating lesions within the cord itself sequences were used with a variety of echo times ( $T_E$  60 ms, 80 ms, 120 ms) and repetition times ( $T_R$  1000 ms, 1500 ms, 2000 ms).

### Measurement of $T_1$ and $T_2$

In many patients calculated images of the NMR relaxation times,  $T_1$  and  $T_2$  were formed. Algorithms supplied by the manufacturer were used to calculate these images from two SE scans and one IR scan ( $\text{SE}_{2000/40}$ ,  $\text{SE}_{2000/120}$ ,  $\text{IR}_{2000/500/40}$ ). The relaxation times could then be read from regions of interest on the displayed image. The validity of these measurements was checked using phantoms filled with  $\text{MnCl}_2$  solution (Johnson *et al.*, 1987). Measurements were then taken from lesions and

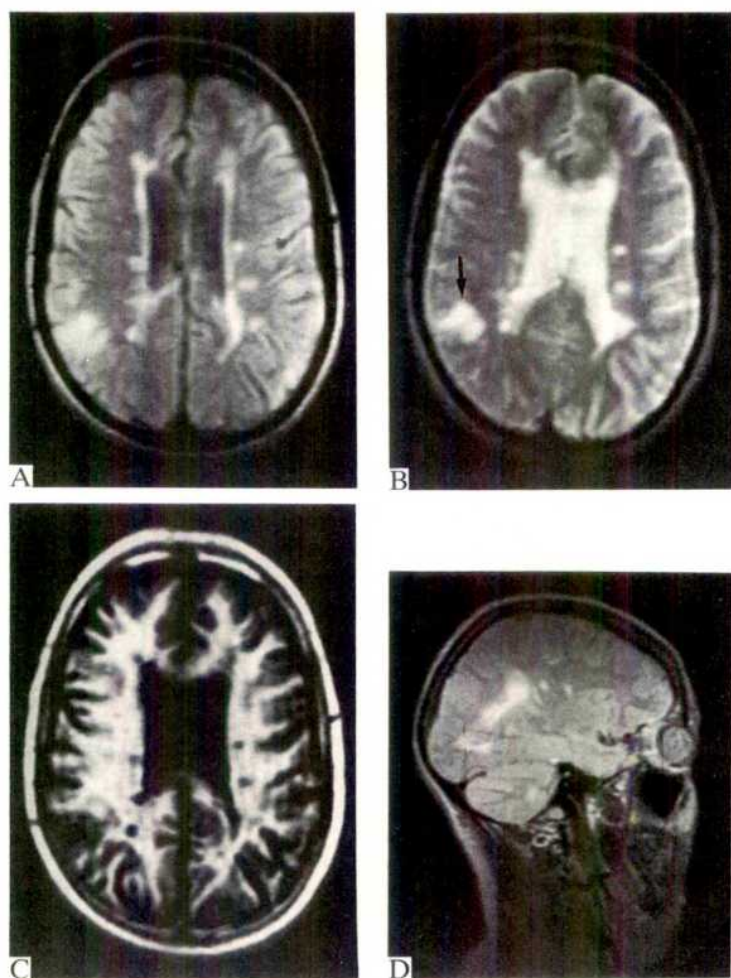


FIG. 1. Male, aged 41 yrs, with clinically definite MS. A, axial SE<sub>2000/40</sub>; B, axial SE<sub>2000/120</sub>; C, axial IR<sub>2000/500/40</sub>; D, sagittal SE<sub>2000/60</sub>. The immediate periventricular changes are best seen with a short echo sequence (A). Discrete cerebral hemisphere lesions are better seen on a long echo sequence (B) and inversion recovery (C). There is a subcortical lesion in the right posterior parietal lesion (arrowed).

normal appearing white matter. Analysis of variance was used to compare measurements made in different sites and in different patient groups.

#### *Repositioning of patients*

Serial examinations were performed in many patients. Accurate repositioning was achieved as follows: three laser light sources were used to position the head. The anteroposterior (AP) angulation of the head was recorded and its position maintained by a band. The first image was a sagittal slice onto which was superimposed a grid with lines corresponding to the position of the slices in subsequent axial imaging sequences. From this pilot image the AP head angulation was recorded as the angle between the vertical and a line drawn between the nasion and the lowest point of the clivus. At subsequent examinations the same AP angulation, as measured by the laser light sources, was

used to position the patient. The level of the axial slices, as defined by the grid superimposed on the image, was adjusted to obtain the same levels as before. The maximum variation in AP angulation between two examinations, as measured from the screen images in 40 patients, was  $+3.6^\circ$  to  $-4^\circ$  (SD  $2^\circ$ ).

#### *Assessment of the number, size and distribution of MRI abnormalities*

Abnormalities were immediately obvious in many patients, but in those presenting with clinically isolated lesions the changes were often less marked. In all patients in those groups, (optic neuritis, brainstem lesions and spinal cord lesions) and in healthy controls, each scan was assessed 'blind' by 4 independent assessors (I.E.C.O., G.H. du B., B.E.K., I.F.M.). In these groups of patients, only those patients whose scans were judged abnormal by all assessors were subsequently classified as such. Equivocal scans, or those where there was not a unanimous decision, were classified as normal. Areas of abnormal signal measuring less than 2 mm in their longest diameter, abnormalities appearing in parts of the image affected by artefact and areas of high signal that could represent the depths of a deep sulcus were excluded. Small areas of heightened signal are often apparent at the frontal horns in normal subjects; thus areas of increased signal in this region were only classified as abnormal if they were larger than 5 mm if symmetric, or if there was a difference of more than 2 mm between the sides.

#### *Quantification of abnormal images*

In order to compare the degree of abnormality in patients with MS and those with clinically isolated neurological lesions a method of quantification of the lesions was required. A method described by Runge *et al.* (1984) proved unsatisfactory because it depended on the assumption of an orderly progression of the distribution of the lesions for which evidence is lacking. Methods of counting individual lesions were useful in patients with only a few discrete lesions but were not suitable for those patients whose scans showed more widespread abnormalities. In such cases lesions were frequently confluent and it proved impossible to resolve reproducibly such areas into separate lesions. We therefore devised a method of assessing the degree of abnormality in a scan which did not depend upon counting individual lesions.

For each patient all slices obtained with a multislice protocol were examined. The periventricular regions were considered separately; lesions which were periventricular in part and extended out into the brain parenchyma were considered 'periventricular', while lesions which were apparently separate from the ventricles were designated 'discrete cerebral lesions'. At times, however, it was difficult to differentiate reliably lesions which were in fact periventricular, protruding from the roof of the lateral ventricle, from those which were discrete from the ventricle and situated in the white matter above the roof. This was particularly the case when axial sections with the standard slice thickness were used alone. The interpretation was often clarified by using additional coronal and sagittal sections. Lesions in the brainstem and cerebellum were assessed separately.

The periventricular region was divided into 7 parts (body of lateral ventricle, frontal horn, trigone, occipital horn, temporal horn, third ventricle and fourth ventricle) and lesions in each were scored 0–3 depending on their size as measured by the maximum degree of penetration from the edge of the ventricle into the surrounding white matter (0 = no lesion, 1 = 5 mm, 2 = 6–10 mm, 3 = > 10 mm).

Discrete lesions separate from the ventricles were scored for each of 8 sites (brainstem, cerebellum, internal capsule, basal ganglia, frontal lobe, parietal lobe, temporal lobe, occipital lobe) and in each site lesions were scored 0–3 on the maximum size in any dimension.

The scores from each of the 15 sites (from each hemisphere when appropriate) were then added to give a cumulative total score, the abnormality score for that study. Scans were independently scored by 2 observers, providing an interrater reliability of 0.95.

*Cerebrospinal fluid*

Polyacrylamide gel electrophoresis (Dr E. J. Thompson) was carried out as previously described (Thompson *et al.*, 1979).

*Patients*

Most of the patients in this investigation were attending the National Hospitals, Queen Square and Maida Vale, or the Moorfields Eye Hospital, City Road. The diagnosis in all patients was reconsidered by a clinical member of the team before the patient was included in the investigation.

## RESULTS

*Multiple sclerosis**Brain abnormalities*

A total of 144 patients with MS were examined by MRI; 114 (aged 24–74 yrs, mean 40 yrs) had clinically definite MS and 30 (aged 24–62 yrs, mean 38 yrs) had clinically probable MS by the criteria of the Poser Committee (Poser *et al.*, 1983). Sagittal MRI examinations of the cervical cord were made in 24 patients with definite MS. All had clinical features of a cord lesion but in none were they acute.

The results of examination of the patients with clinically definite MS are summarized in Table 1. Regions of abnormal periventricular signal were demonstrated in 112 of the 114 patients. In 1 of the 2 patients without periventricular lesions there were areas of abnormal signal only in the brainstem and in the other patient no abnormalities were seen. The former had suffered 3 clinical episodes with remission which comprised 1 episode of brainstem disturbance, 1 episode of optic neuritis and an episode of lower limb sensory disturbance. The latter patient had experienced 2 clinical episodes, 1 with clinical evidence of a cervical cord lesion; the other was an episode of acute unilateral optic neuritis.

The periventricular white matter adjacent to the trigones and bodies of the lateral

TABLE 1. DISTRIBUTION OF MRI ABNORMALITIES  
IN 114 PATIENTS WITH CLINICALLY  
DEFINITE MULTIPLE SCLEROSIS

| <i>Site of abnormalities</i>         | <i>n</i> | <i>%</i> |
|--------------------------------------|----------|----------|
| Periventricular (lateral ventricles) | 112      | 98       |
| Trigone                              | 109      | 96       |
| Body of lateral ventricle            | 109      | 96       |
| Frontal horn                         | 83       | 73       |
| Occipital horn                       | 95       | 83       |
| Temporal horn                        | 67       | 59       |
| Third ventricle                      | 39       | 34       |
| Fourth ventricle                     | 68       | 60       |
| Discrete cerebral white matter       | 102      | 90       |
| Basal ganglia                        | 29       | 25       |
| Internal capsule                     | 13       | 11       |
| Brainstem                            | 77       | 68       |
| Cerebellum                           | 56       | 49       |
| Any cerebral abnormality             | 113      | 99       |

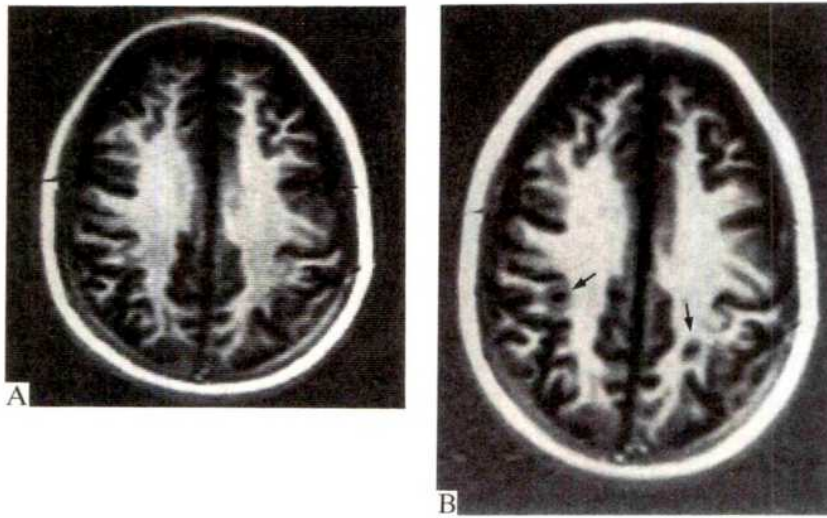


FIG. 2. Serial images (IR<sub>2000</sub> 600.40) of a 30-yr-old woman with MS. The initial scan (A) was normal. Ten weeks later (B) there were 2 new lesions (arrowed) which have a 'halo' appearance.

ventricles was most frequently involved (96%; fig. 1), followed by that around the occipital (83%) and frontal horns (73%). Lesions in the floor of the fourth ventricle were seen in 60% of patients but around the third ventricle in only 34%. Lesions discrete from the ventricles were seen in cerebral white matter in 90% (fig. 1), the majority in the white matter of the frontal and parietal lobes above the level of the bodies of the lateral ventricles, in the centrum semiovale. Lesions were present in the basal ganglia in 25% and in the internal capsule in 11%. Infratentorially, lesions were seen more commonly in the brainstem (68%) than in the cerebellar hemispheres (49%).

All 30 patients with clinically probable MS had abnormal scans. When the frequency and distribution of lesions in 30 patients with clinically definite MS were compared with those in clinically probable cases, there was no significant difference in the incidence of periventricular lesions (present in all cases) or of discrete cerebral white matter lesions between the 2 groups ( $P < 0.2$ ; analysis of variance). Cerebellar ( $P < 0.005$ ) and brainstem ( $P < 0.05$ ) lesions were, however, more commonly seen in patients with definite MS.

A comparison was made between the distribution of lesions in patients with and without oligoclonal IgG bands in the CSF, which were present in 37/49 (76%) of the 114 patients with clinically definite MS. Brainstem lesions were commoner ( $P = 0.05$ ) in patients with oligoclonal bands, but there was no difference for lesions in other sites. The presence of oligoclonal bands was also associated with a significantly higher abnormality score (i.e., with more extensive cerebral involvement,  $P = 0.05$ ). The association of oligoclonal bands with brainstem lesions probably reflects the greater likelihood of brainstem lesions being frequent in clinically



definite disease. Oligoclonal bands were present in the 1 patient with definite MS in whom no abnormalities were seen on MRI.

Nine patients with clinically definite disease had lesions in which the centre was of different signal intensity from the periphery, producing a halo-like appearance (fig. 2). On the SE sequences ( $SE_{2000/120}$ ) these lesions had a centre of higher signal than the periphery with the reverse effect on the IR sequence ( $IR_{2000/600/40}$ ). These findings suggested that the centre of the lesion was of longer  $T_1$  and  $T_2$  than the periphery, a prediction confirmed by measurement of  $T_1$  and  $T_2$  from calculated images. In 2 of the 9 patients there was evidence that the lesions may have been of recent origin. The patient illustrated in fig. 2 had a previous episode of optic neuritis and was scanned after an episode attributable clinically to a lesion in the spinal cord. A repeat examination ten weeks later showed 2 new areas of abnormal signal which were not present in the same slice at the earlier examination. The patient had suffered no new symptoms in this period. These findings are further considered in the discussion.

### *Spinal cord abnormalities*

All 24 patients in whom a satisfactory examination of the cervical spinal cord was achieved had periventricular lesions and 20 also had discrete lesions in the cerebral white matter.

SE images of the cervical cord were made in the sagittal plane using the standard head receiver coil as supplied by the manufacturer, rather than surface receiver coils. Areas of high signal within the cord, probably due to an increased  $T_2$  (although relaxation times were not calculated), were seen in 14/24 patients. In 1 patient there was an apparent fusiform enlargement of the cervical cord. The areas of altered signal were of varying appearance: in 8 patients the abnormalities extended longitudinally over one or more segments (fig. 3), in 2 the whole transverse diameter of the cord appeared abnormal, and in 6 the lesions were more rounded in shape and did not appear to extend along the long axis of the cord.

### *Follow-up MRI examinations*

Seventeen patients with clinically definite MS had repeat MRI examination performed approximately three months following the first examination (8–19 wks, mean 12 wks). The patients were carefully repositioned (*see Methods*) and the sequences used for the first examination repeated. Seven showed lesions on the second scan which had not been on the earlier study (fig. 2). In 2 the follow-up scan failed to demonstrate a lesion which had been seen on the first examination, although both showed new lesions which had not been seen on the first examination.

Many of the lesions showed changes in signal intensity or size when the images of the two studies were compared. Change in intensity alone was difficult to evaluate since it is dependent on a number of factors and  $T_1$  and  $T_2$  of the lesions were not measured in all cases. Minor changes in size of the lesions were also difficult to

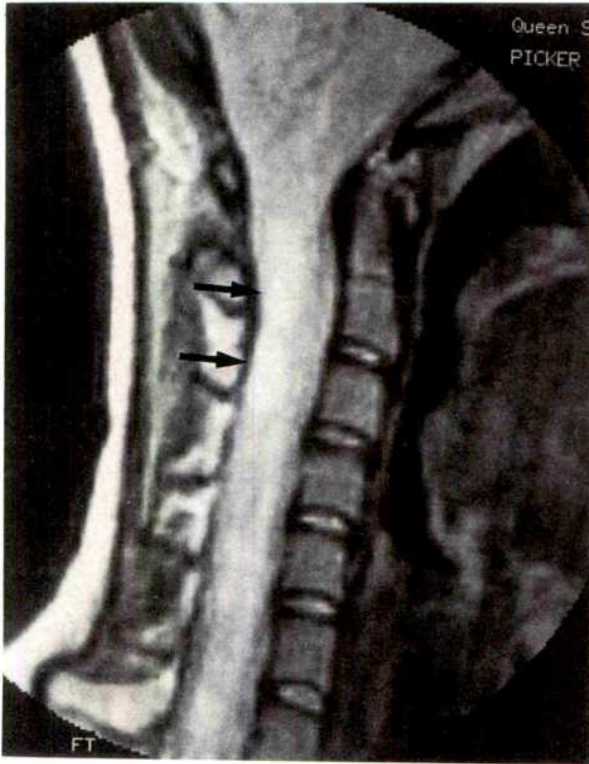


FIG. 3. Sagittal image ( $SE_{1500/90}$ ) of the cervical cord in a 28-yr-old female with definite MS. There are 2 regions of increased signal in the cord at C2 and C3 (arrowed).

evaluate as slight alterations in section level might cause considerable alterations in the appearance of the lesion. The results of reexamining patients with clinically probable MS will be reported in a later paper.

#### *Measurement of relaxation times ( $T_1$ and $T_2$ )*

Measurements of relaxation times were made in 34 patients with clinically definite MS and in the 18 control subjects in whom the necessary sequences had been performed. In the patients, readings were taken from the areas of visibly abnormal signal intensity and from apparently normal brain, in both white matter and grey matter (Tables 2, 3, 4). There was a wide variation in relaxation times of the lesions. For periventricular lesions,  $T_1$  ranged from 455 ms to 1785 ms and  $T_2$  ranged from 125 ms to 405 ms, while for discrete lesions within the cerebral white matter  $T_1$  ranged from 185 ms to 480 ms and  $T_2$  ranged from 110 ms to 220 ms. The relaxation time values were longer for lesions which were periventricular in site than for those which were in the cerebral white matter (analysis of variance,  $P < 0.05$ ).

The values obtained for  $T_1$  and  $T_2$  in the healthy controls are shown in Tables 3 and 4, respectively. A comparison of these values of  $T_1$  and  $T_2$  with those for the normal appearing white matter in the patients with MS was made. The values in the patients were significantly higher in all cerebral hemisphere lobes studied (Tables 3, 4). The implications of these results are considered in the Discussion.

TABLE 2. MEAN RELAXATION TIMES OF LESIONS IN THE BRAIN IN 34 PATIENTS WITH MULTIPLE SCLEROSIS\*

| Brain region   | Discrete white matter lesions |          | Periventricular lesions |          |
|----------------|-------------------------------|----------|-------------------------|----------|
|                | $T_1$                         | $T_2$    | $T_1$                   | $T_2$    |
| Temporal lobe  | 489 (92)                      | 127 (28) |                         |          |
| Occipital lobe | 486 (19)                      | 112 (21) | 714 (202)               | 205 (82) |
| Frontal lobe   | 541 (57)                      | 139 (23) | 623 (137)               | 164 (49) |
| Parietal lobe  | 567 (87)                      | 150 (53) | 627 (172)               | 179 (86) |
| Brainstem      | 608 (72)                      | 129 (22) |                         |          |
| Cerebellum     | 542 (56)                      | 106 (14) |                         |          |

\* Mean values in ms; SD in brackets.

TABLE 3. MEAN  $T_1$  MEASUREMENTS (IN ms, SD BRACKETED) OF APPARENTLY NORMAL WHITE AND GREY MATTER IN MULTIPLE SCLEROSIS PATIENTS (n = 34) AND CONTROL SUBJECTS (n = 18)

|                | White matter          |                       | Grey matter |          |
|----------------|-----------------------|-----------------------|-------------|----------|
|                | MS                    | Controls              | MS          | Controls |
| Temporal lobe  | 429 (31) <sup>1</sup> | 400 (22) <sup>1</sup> | 602 (48)    | 615 (45) |
| Occipital lobe | 430 (44) <sup>2</sup> | 395 (21) <sup>2</sup> | 581 (49)    | 576 (40) |
| Frontal lobe   | 421 (37) <sup>2</sup> | 385 (21) <sup>2</sup> | 616 (45)    | 604 (41) |
| Parietal lobe  | 427 (35) <sup>3</sup> | 397 (20) <sup>3</sup> | 602 (28)    | 579 (36) |

<sup>1</sup>  $P = 0.05$ ; <sup>2</sup>  $P = 0.001$ ; <sup>3</sup>  $P = 0.01$ .TABLE 4. MEAN  $T_2$  MEASUREMENTS (IN ms, SD BRACKETED) OF APPARENTLY NORMAL WHITE AND GREY MATTER IN MULTIPLE SCLEROSIS PATIENTS (n = 34) AND CONTROL SUBJECTS (n = 18)

|                | White matter         |                      | Grey matter |          |
|----------------|----------------------|----------------------|-------------|----------|
|                | MS                   | Controls             | MS          | Controls |
| Temporal lobe  | 94 (10) <sup>1</sup> | 87 (9) <sup>1</sup>  | 109 (18)    | 104 (13) |
| Occipital lobe | 93 (17) <sup>2</sup> | 88 (10) <sup>2</sup> | 101 (12)    | 100 (12) |
| Frontal lobe   | 95 (10) <sup>3</sup> | 86 (7) <sup>3</sup>  | 111 (11)    | 108 (15) |
| Parietal lobe  | 98 (12) <sup>4</sup> | 90 (9) <sup>4</sup>  | 111 (8)     | 103 (14) |

<sup>1</sup>  $P = 0.1$ ; <sup>2</sup>  $P = 0.1$ ; <sup>3</sup>  $P = 0.04$ ; <sup>4</sup>  $P = 0.01$ .

### *MRI of postmortem brains*

It is obvious that the distribution of lesions at MRI corresponds with that recognized pathologically (Cruveilhier, 1829–1842; Charcot, 1868; Gowers, 1893; Dawson, 1916; Hallervorden, 1940; Fog, 1965; Lumsden, 1970; Allen, 1984). It was nevertheless important to establish in individual cases whether the abnormal areas on the images do indeed correspond to plaques. There is no published example of histological confirmation of the nature of lesions recognized in vivo by MRI in a patient with MS. Stewart *et al.* (1984) showed that reasonable images can be obtained from postmortem material. We therefore examined 6 formalin-fixed brains



from patients dying with clinically definite MS; 4 were male (aged 51, 52, 56 and 78 yrs) and 2 female (56 and 67 yrs). After removal the brains were weighed and examined for the presence of external abnormalities and quickly immersed in 30% neutral formaldehyde. After a period of fixation varying between 2 and 3 wks, the brains were further examined and subsequently secured, vertex down, to the base of a perspex cradle. The imaging plane was perpendicular to the base. Serial near-contiguous images were obtained in an approximately coronal plane using the multislice technique and SE sequences (SE<sub>1500/40</sub>).

After the NMR observations the brains were cut. The first coronal section was made through the mamillary bodies while the brain was still attached to the base and care was taken to cut exactly perpendicularly to the base of the apparatus. After the first cut, 0.5 or 1 cm thick sections were cut through the whole brain. Each section was examined and matched with the corresponding NMR picture (fig. 4). Finally, blocks were taken from various regions which included areas with normal-looking myelin and plaques. From paraffin embedded blocks, sections were cut and stained with haematoxylin and eosin, haematoxylin-van Gieson, luxol fast blue, Gies-Marsland silver impregnation for axons, and Holzer for glial fibres. Some blocks were embedded in celloidin and sections from them stained for myelin.

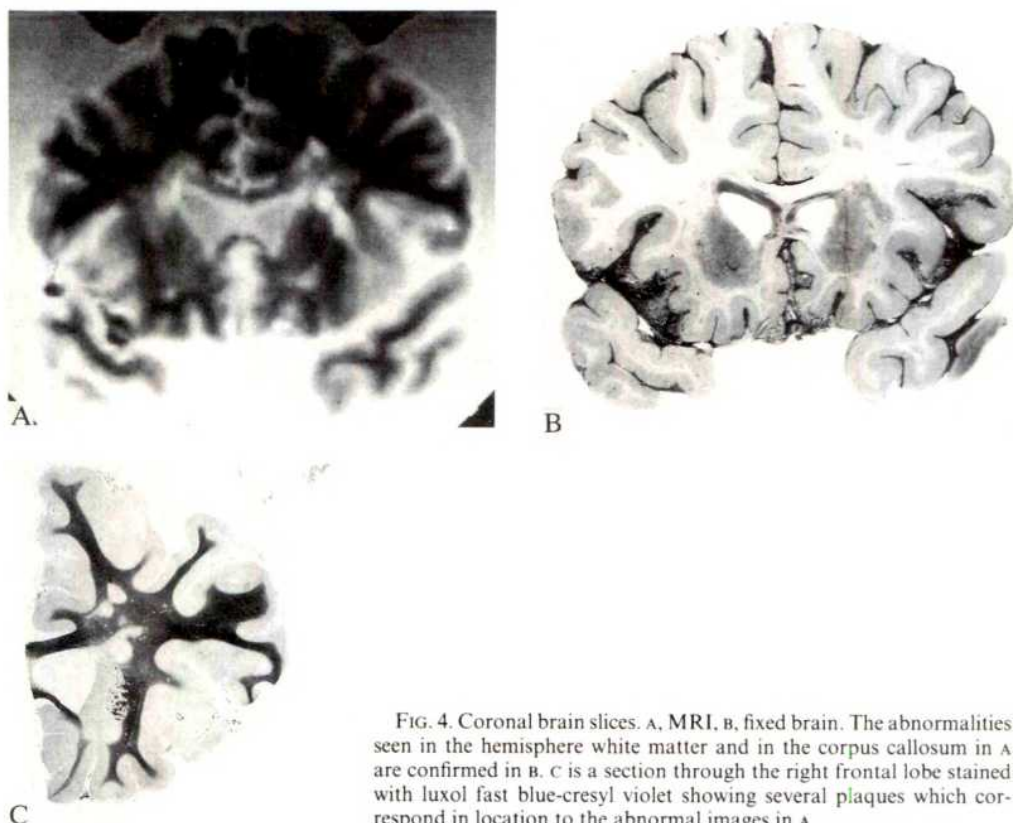


FIG. 4. Coronal brain slices. A, MRI, B, fixed brain. The abnormalities seen in the hemisphere white matter and in the corpus callosum in A are confirmed in B. C is a section through the right frontal lobe stained with luxol fast blue-cresyl violet showing several plaques which correspond in location to the abnormal images in A.

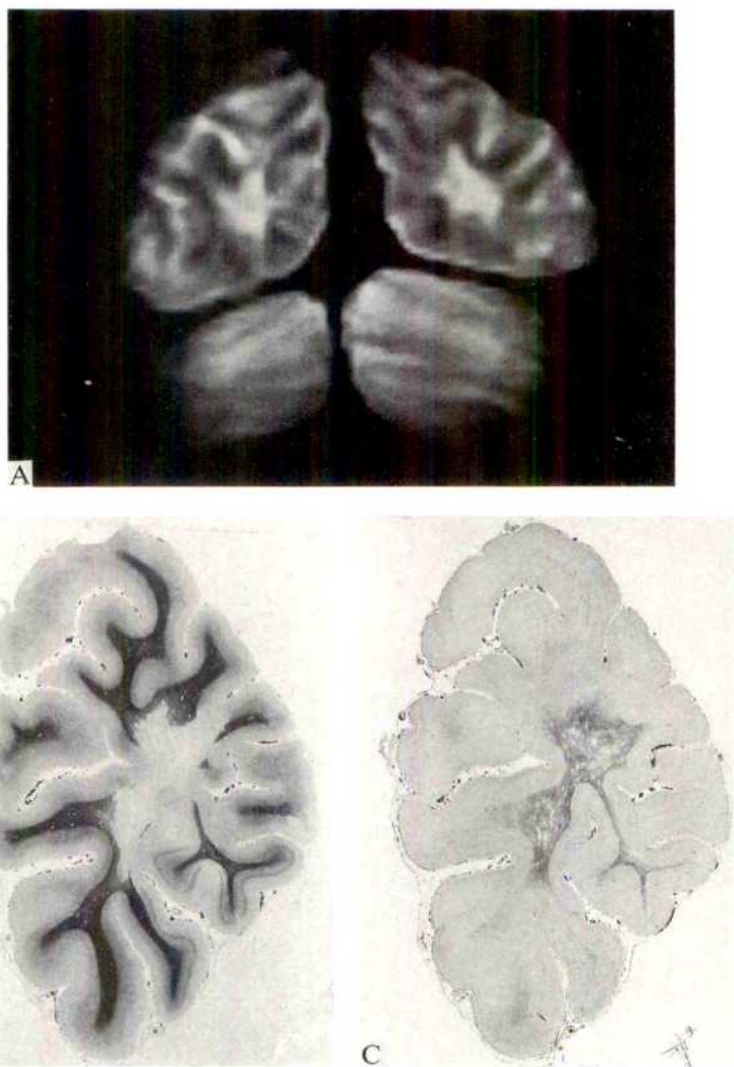


FIG. 5. MRI (A) of the occipital lobes and cerebellum showing symmetric areas of abnormal signal in the former. B and C are sections through the left occipital lobe showing demyelination (B) and dense gliosis (C) corresponding to the abnormal image (A).

All the brains were of normal shape but 2 of them (both males, aged 51 and 78 yrs) were moderately atrophic (1195 and 1110 g, respectively). The leptomeninges were thin and transparent; the atrophic brains had wide sulci. At the base the vessels were of normal configuration and, on occasion, showed slight to moderate atherosclerosis. The cranial nerves were normal. In 2, plaques could be seen on the ventrolateral surface of the pons: they appeared slightly depressed, grey and, in places, serpiginous. In all the cases the cortical ribbon and deep grey matter looked normal. The lateral ventricles showed a mild degree of dilatation; plaques were

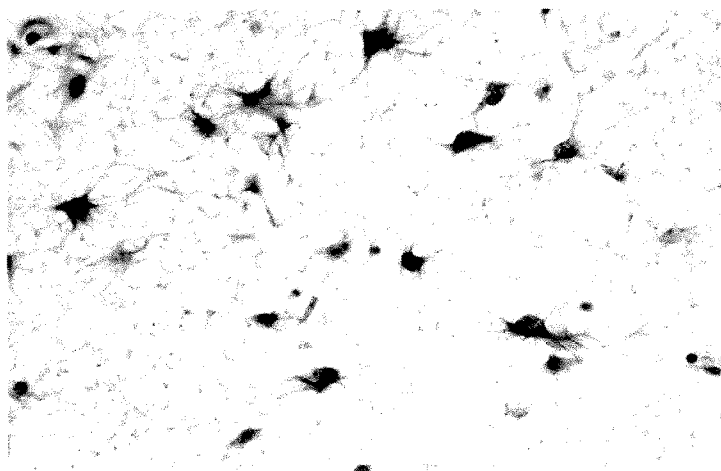


FIG. 6. Marked astrocytic hyperplasia. The cell bodies of the astrocytes stain with GFAP. PAP method,  $\times 300$ .

seen in all cases, some of them deeply situated in the hemisphere white matter, while others were arranged around the lateral ventricles. When they involved the corpus callosum this was thin and grey. Occasionally, plaques were also seen to impinge into the cortical and subcortical grey matter which appeared pearl grey.

Histological examination of the plaques showed a varying degree of myelin loss, which was in places complete, as well as astrocytic gliosis. Comparing sections stained for myelin and glial fibres (fig. 5B, C) it appeared that in the same plaque the loss in myelin staining corresponded to a proportional increase in intensity of the glial proliferation. The transition between myelinated and demyelinated areas was usually abrupt, but occasionally there was an intervening zone in which the myelin stain was pale but still present. Silver impregnation showed the axons to be relatively spared although in some areas of myelin pallor or loss they were severely reduced in number or almost completely absent. Oligodendrocytes were also reduced in number. Indeed, in some of the most severely affected areas they were completely absent, and the only cells present were fibrillary astrocytes (fig. 6) whose processes formed a delicate network of fibres, particularly dense around blood vessels and in periventricular regions. In the areas of most severe myelin loss, blood vessels appeared singly or forming small groups; they had thick fibrous walls and were surrounded by enlarged spaces; some of them were cuffed with lymphocytes and occasional plasma cells.

As fig. 4 shows, there was a good correspondence between the areas of abnormality in the NMR images and the histological lesions, although the outlines were not precisely the same. This difference is to be expected, since the NMR image represents averaging of the signal over a slice 10 mm thick whereas the histological sections were  $30\text{ }\mu\text{m}$  thick.

We conclude that MRI abnormalities originated from chronic plaques of MS.

*Optic neuritis*

Optic neuritis is one of the commonest isolated manifestations of MS. In the United Kingdom, the majority of patients presenting with this clinical syndrome ultimately develop the generalized disease (McDonald, 1983). It is therefore of considerable interest to know the frequency with which multiple lesions are found at presentation. We have investigated 51 patients fulfilling the criteria of Gould *et al.* (1977) for acute optic neuritis. Those with symptoms of previous ocular disease or neurological symptoms, and those with evidence of other causes for optic neuropathy (e.g., ischaemia) were excluded. Further details of some aspects of our observations on a smaller series of patients have been reported previously (Ormerod *et al.*, 1986c).

Particular interest attaches to the adult patients presenting with their first episode of acute 'isolated' unilateral optic neuritis. Of such patients, 29/42 scanned 1 to 40 wks after onset (mean 9 wks) had multiple brain lesions (fig. 7). In 28 there were periventricular abnormalities; 21 patients showed additional discrete lesions elsewhere in the cerebral white matter; 1 patient showed only discrete lesions.

In order to assess the sensitivity of MRI in detecting multiplicity of lesions the results were compared with those obtained from somatosensory (SEP) and brainstem auditory (BAEP) evoked potentials in 29 patients. The overall incidence of EP abnormalities (8/29, 28%) was similar to that reported by others (Matthews

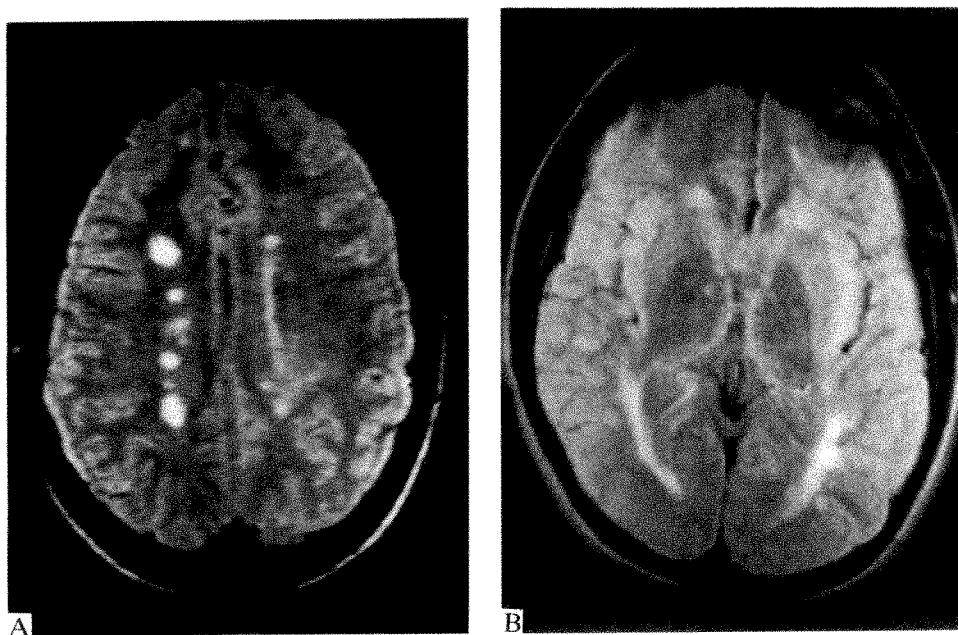


FIG. 7. SE<sub>2000 60</sub> axial images showing brain lesions in 2 patients with isolated optic neuritis. A, a 27-yr-old male with acute unilateral optic neuritis of 1 w's duration. B, a 41-yr-old male with bilateral sequential optic neuritis. There is involvement of the optic radiation.

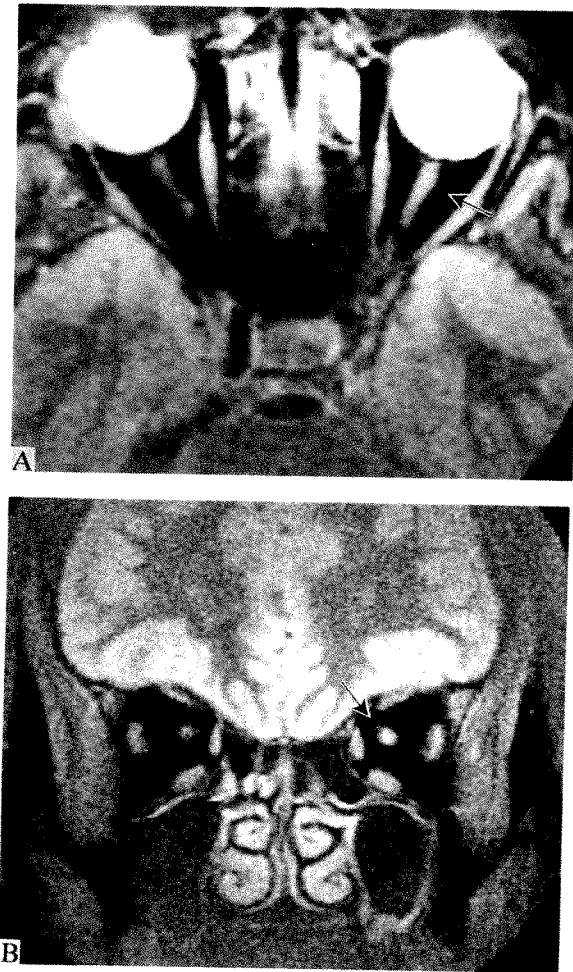


FIG. 8. A, axial, and B, coronal orbital images ( $IR_{1500\ 150\ 40}$ ) in a 36-yr-old female with a 2-wk history of left optic neuritis. There is increased signal in the anterior portion of the left optic nerve (arrowed).

*et al.*, 1982; Sanders *et al.*, 1984) and much lower than that detected by MRI (19/31, 61%). In contrast, the evoked potential method was more sensitive than MRI in detecting lesions in the optic nerve itself: visual evoked potentials (VEPs) were abnormal in all our patients. At the time of our previous paper (Ormerod *et al.*, 1986c) we had failed to demonstrate any abnormalities in the optic nerve by MRI. However, the recent application of the STIR sequence and surface coils have enabled us to obtain good axial and coronal images of the optic nerves, and we have so far seen 10 lesions in 14 patients following an attack of acute unilateral optic neuritis (fig. 8) (Miller *et al.*, 1986).

#### *Serial observations*

Because of the similarity between the frequency of MS after isolated optic neuritis in the United Kingdom (range 42–85%, higher frequencies being observed with longer follow up; McDonald, 1983) and the frequency of finding multiple lesions



in MR images at presentation, it is tempting to suggest that the patients with multiple lesions already have MS. This conclusion is not, however, justified at present on the basis of a single scan, since the frequency with which optic neuritis may be the sole symptomatic manifestation of what in reality is a multifocal but nevertheless monophasic pathological process (i.e., a form of acute disseminated encephalomyelitis) is unknown. There is evidence that such cases can occur in children in whom the subsequent development of MS is very uncommon (Meadows, 1969; Parkin *et al.*, 1984). If after an interval of greater than one month (in keeping with the diagnostic criteria of Poser *et al.*, 1983) new lesions could be demonstrated, the diagnosis would become more likely. We therefore undertook a serial clinical and MRI study of the patients presenting with optic neuritis.

Twenty-five adults have been rescanned after 5 to 20 months (Table 5). Five showed unequivocal evidence of new abnormalities in the images. In these patients, the criteria for a diagnosis of clinically probable MS are fulfilled (Poser *et al.*,

TABLE 5. FOLLOW-UP STUDIES IN OPTIC NEURITIS

|                           | <i>New lesions</i><br>( <i>follow-up brain MRI</i> ) | <i>Clinical relapse</i> |
|---------------------------|------------------------------------------------------|-------------------------|
| Abnormal initial MRI (17) | 3                                                    | 6                       |
| Normal initial MRI (8)    | 2                                                    | 0                       |

1983). Six other patients had experienced a relapse attributable to a lesion outside the optic nerve, although none of these had a new lesion visible at follow-up; in these cases, the criteria for a clinically definite diagnosis were fulfilled: all 6 had multiple brain lesions at presentation. None of the 8 with a normal initial scan had further symptoms at follow-up.

#### *Isolated brainstem lesions*

An isolated brainstem disturbance is a common initial manifestation of MS. However, it is not known what proportion of patients presenting with such a brainstem disturbance will ultimately develop MS. MRI is clearly of interest in such patients to identify the symptomatic lesion and to establish the frequency of multiple lesions at presentation. We therefore examined 44 consecutive patients with clinical evidence of an isolated brainstem abnormality by MRI. None had had previous neurological disturbances. All were in the age range where the first episode of MS could be the cause of their illness (15–55 yrs).

Of the 44 patients scanned, a diagnosis other than MS was made in 4; 3 of these had sixth cranial nerve palsies with additional long tract signs. One female with a 2-wk history of diplopia had a pontine angioma; another female with a 6-month history of diplopia had a brainstem glioma (fig. 9A); and a 38-yr-old male with a 5-wk history of progressively worsening diplopia had a pontine haematoma (fig. 9B).

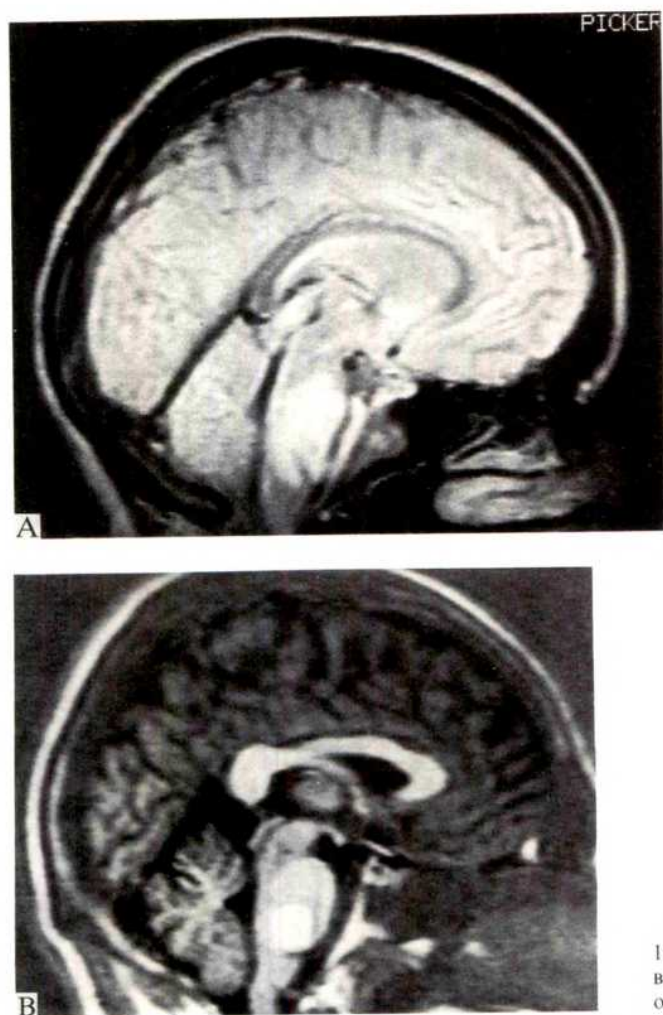


FIG. 9. A, sagittal image ( $SE_{2000\ 60}$ ) of an 18-yr-old female with a brainstem glioma. B, sagittal image ( $IR_{2000\ 500\ 40}$ ) of a 38-yr-old male with a pontine haematoma.

The fourth patient, a female of 20 yrs who had respiratory failure and upbeat nystagmus, had extensive lesions in the medulla and in both thalami thought to be due to Leigh's disease.

The remaining 40 patients had a variety of brainstem disturbances (Table 6). For example, all those with downbeat or torsional nystagmus had nystagmus in other directions and 3 with gaze palsies had a one-and-a-half syndrome. The severity of the abnormalities varied. Thus some patients with an internuclear ophthalmoplegia had a full range of adduction of the eye on the affected side but velocity was reduced, while others had a complete failure of adduction.

The mean age of these 40 patients was 33 yrs (20–52 yrs); 20 were male and 20 female. There was a wide range in the duration of the brainstem dysfunction (1 wk–12 yrs), but this range fell into two clear groups without overlap. Twenty-six patients had had symptoms for less than 3 months (mean 3.6 wks) and 14 patients

TABLE 6. CLINICAL FEATURES IN 40 PATIENTS WITH ISOLATED BRAINSTEM LESIONS

|                                  | <i>n</i> | %  |
|----------------------------------|----------|----|
| Horizontal nystagmus*            | 23       | 58 |
| Upbeat nystagmus*                | 14       | 35 |
| Downbeat or torsional nystagmus* | 7        | 18 |
| Internuclear ophthalmoplegia     |          |    |
| Unilateral                       | 6        | 15 |
| Bilateral                        | 7        | 18 |
| Gaze palsy                       | 6        | 15 |
| One-and-a-half syndrome          | 3        | 7  |
| Unilateral VI nerve palsy        | 5        | 13 |
| Bilateral VI nerve palsy         | 2        | 5  |
| Unilateral VII nerve palsy       | 5        | 13 |
| Bilateral VII nerve palsy        | 2        | 5  |

\* 1st, 2nd, or 3rd degree.

had symptoms for more than 9 months (mean 20 months). There was no significant difference in the ages of the two groups, the former having a mean age of 31 yrs (20–47 yrs) and the latter 34 yrs (22–52 yrs).

Thirty-five of the 40 patients (88%) had a lesion demonstrated in the brainstem by MRI (Table 7). There was a good correlation between the clinical picture and the site of the lesion in the case of cranial nerve palsies (6th, 7th) and the one-and-a-half syndrome (fig. 10). The majority of patients with internuclear ophthalmoplegia also had lesions that could involve the medial longitudinal fasciculus (fig. 11), but care must be exercised here as lesions in the floor of the fourth ventricle were so common that a lesion is likely to be found in the region of the medial longitudinal fasciculus even in those patients who do not have an internuclear ophthalmoplegia. Thirty of the 40 undiagnosed patients (75%) had MRI evidence of disseminated lesions in the periventricular region, or discretely in the cerebral hemisphere, or usually both (Table 7). The distribution resembled that seen in MS. The presence of multiple lesions was unrelated to the duration of symptoms.

TABLE 7. MRI ABNORMALITIES IN 40 PATIENTS WITH ISOLATED BRAINSTEM LESIONS

|                                                             | <i>BS</i> | <i>C</i> | <i>Only P</i> | <i>Only DC</i> | <i>P + DC</i> | <i>Any cerebral abnormality</i> |
|-------------------------------------------------------------|-----------|----------|---------------|----------------|---------------|---------------------------------|
| Duration of symptoms less than 3 months ( <i>n</i> = 26)    |           |          |               |                |               |                                 |
| Number                                                      | 23        | 6        | 5             | 1              | 14            | 20                              |
| %                                                           | 88        | 26       | 19            | 4              | 54            | 77                              |
| Duration of symptoms greater than 9 months ( <i>n</i> = 14) |           |          |               |                |               |                                 |
| Number                                                      | 12        | 3        | 1             | 0              | 9             | 10                              |
| %                                                           | 86        | 21       | 7             | 0              | 64            | 71                              |

BS = brainstem; C = cerebellum; P = periventricular; DC = discrete cerebral.



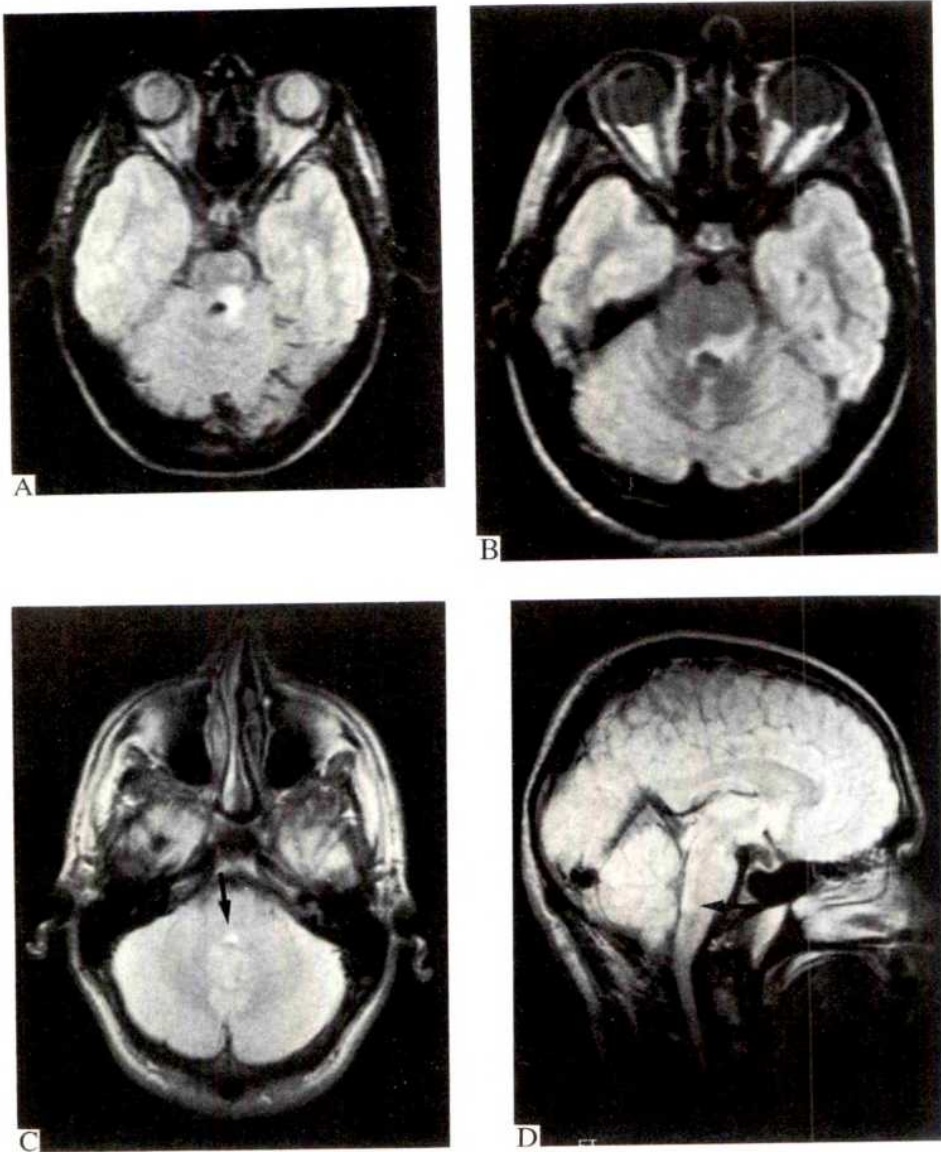


FIG. 10. A, axial slice ( $SE_{2000,60}$ ) from a 25-yr-old male with a 4-wk history of diplopia and ataxia. Examination revealed a left one-and-a-half syndrome, and left facial weakness. There is a left-sided lesion in the floor of the fourth ventricle, extending to the midline. B, axial slice ( $SE_{2000,60}$ ) of a 29-yr-old female with a 2-wk history of diplopia, ataxia and left facial numbness. Examination revealed horizontal and upbeat nystagmus and left facial sensory loss. There is a lesion in the floor of the fourth ventricle extending into the left posterolateral pons. C, axial, and D, sagittal slices ( $SE_{2000,60}$ ) of a 30-yr-old male with bilateral sixth nerve palsies of 2 wks duration. There is a midline lesion in the floor of the fourth ventricle (arrowed).

The sensitivity of MRI in detecting lesions was compared with that of evoked potential methods. In the brainstem itself lesions were detected by BAEPs in 7 of the 32 patients and by SEPs following median nerve stimulation at the wrist in 5 of 31 patients, 4 of whom also had an abnormal BAEP (Table 8). MRI, which was

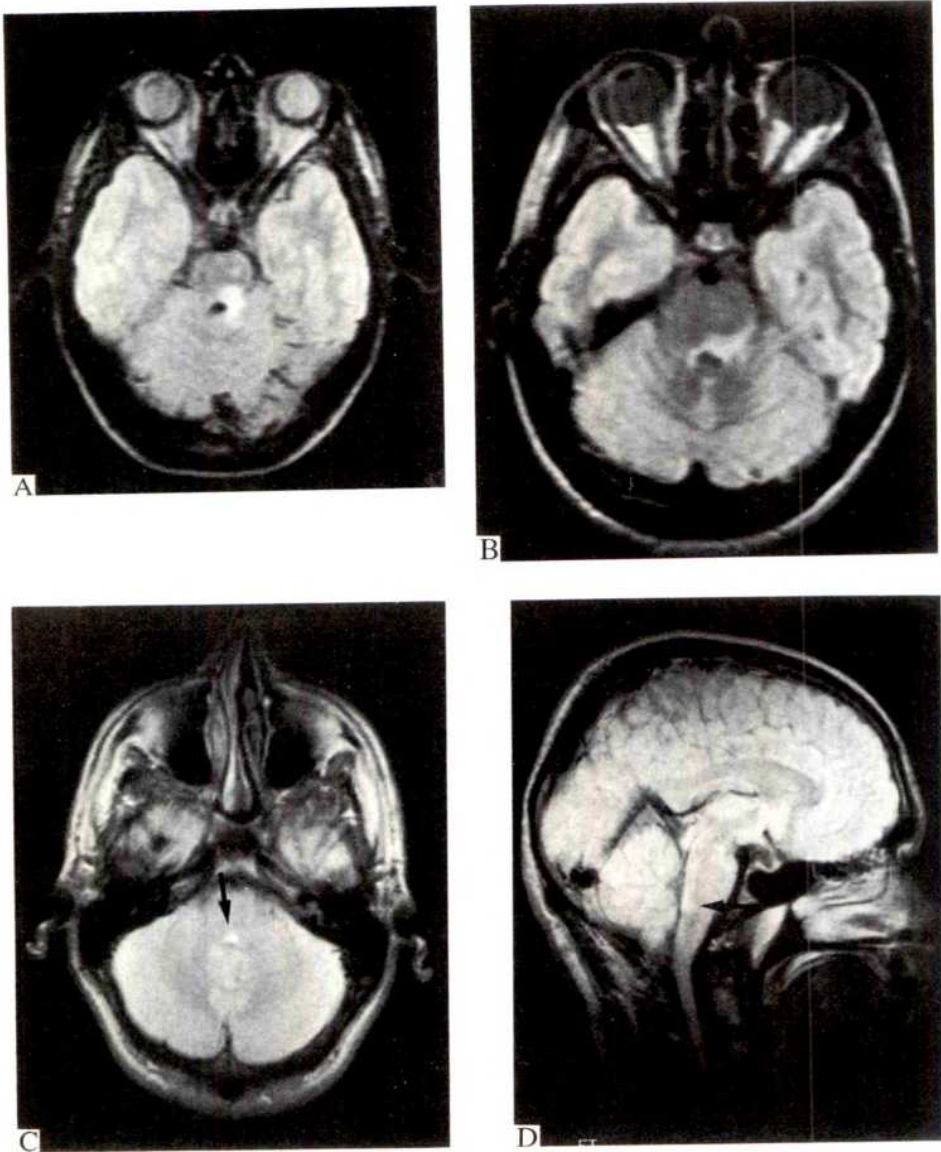


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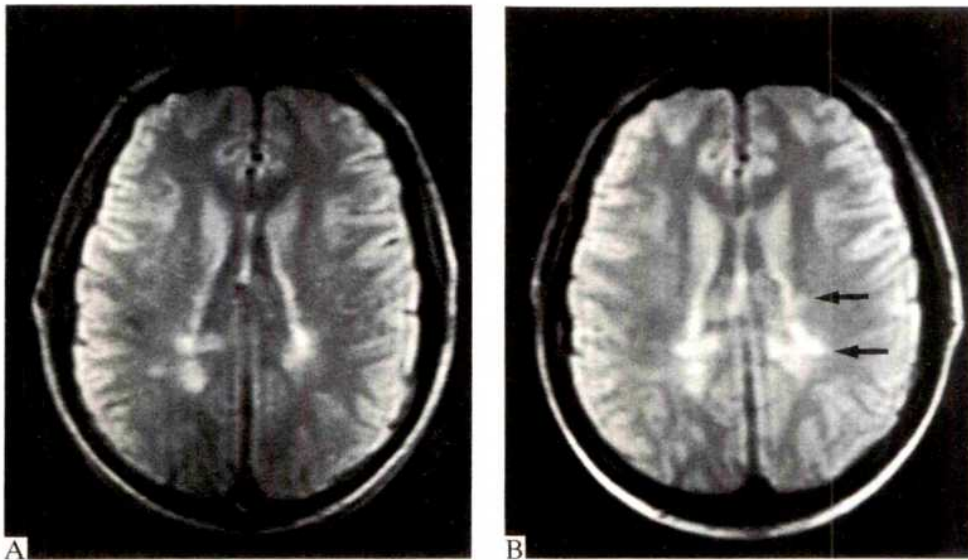


FIG. 12. A, a 47-yr-old male who presented with an acute brainstem lesion that remitted. Periventricular lesions are seen ( $SE_{2000/60}$ ). B, follow-up scan 1 yr later shows several new periventricular lesions (arrowed).

### *Isolated spinal cord syndromes*

Thirty-four patients with clinically isolated lesions of the spinal cord were examined, 23 with a chronic progressive syndrome (aged 25–50 yrs, mean 41), and 11 with an acute presentation, that is, evolution of the syndrome over less than 2 wks (aged 15–35 yrs, mean 27). In those with a chronic syndrome the most common presentation was with a progressive spastic paraparesis or tetraparesis without a sensory level and often with little alteration in sensation. Of those with an acute presentation all had sensory symptoms and 7/11 had a sensory level detectable at some stage in the illness. Only 1 had a syndrome of complete transverse

TABLE 8. RESULTS OF EVOKED POTENTIAL AND CSF EXAMINATION IN PATIENTS WITH BRAINSTEM LESIONS

|                                            | <i>VEP</i> |          | <i>AEP</i> |          | <i>SEP</i> |          | <i>Oligoclonal CSF IgG bands</i> |    |
|--------------------------------------------|------------|----------|------------|----------|------------|----------|----------------------------------|----|
|                                            | <i>N</i>   | <i>A</i> | <i>N</i>   | <i>A</i> | <i>N</i>   | <i>A</i> | —                                | +  |
| Duration of symptoms less than 3 months    |            |          |            |          |            |          |                                  |    |
| Number                                     | 19         | 4        | 18         | 3        | 17         | 2        | 11                               | 9  |
| %                                          | 83         | 17       | 86         | 14       | 90         | 10       | 55                               | 45 |
| Duration of symptoms greater than 9 months |            |          |            |          |            |          |                                  |    |
| Number                                     | 7          | 7        | 7          | 4        | 9          | 3        | 6                                | 5  |
| %                                          | 50         | 50       | 64         | 36       | 75         | 25       | 57                               | 43 |

VEP=visual evoked potential; AEP=auditory evoked potential; SEP=somatosensory evoked potential; N=normal; A=abnormal.



TABLE 9. INCIDENCE OF ABNORMALITIES IN CSF AND EVOKED POTENTIALS IN CLINICALLY ISOLATED SPINAL CORD SYNDROMES

|          | <i>Oligoclonal CSF<br/>IgG pattern</i> | <i>VEP</i> | <i>AEP</i> | <i>SEP</i> |
|----------|----------------------------------------|------------|------------|------------|
| Acute    |                                        |            |            |            |
| Cervical | 0/5                                    | 0/3        | 0/3        | 0/3        |
| Thoracic | 0/4                                    | 0/2        | 0/2        | 0/2        |
| Chronic  |                                        |            |            |            |
| Cervical | 2/4                                    | 0/5        | 0/5        | 1/5        |
| Thoracic | 3/13                                   | 1/13       | 2/13       | 3/13       |

VEP=visual evoked potential; AEP=auditory evoked potential; SEP=somatosensory evoked potential.

myelitis. Patients with a previous history of neurological disturbance or with physical signs suggestive of lesions outside the spinal cord were excluded. All patients with chronic syndromes and 7/11 with acute syndromes had myelography. Those in whom external compression of the cord had been demonstrated were excluded. The patients underwent MRI examination of the spinal cord and the brain. The results were compared with those obtained from evoked potential studies and with the CSF findings.

MRI demonstrated lesions within the brain in 4/11 patients with acute syndromes and in 14/23 with a chronic syndrome. The form and distribution of the abnormalities in the brain were similar to those in MS.

Visual, auditory and somatosensory evoked potential examinations were performed in 23 patients including 12/18 in whom lesions were seen on the cerebral MRI examinations (Table 9). Evoked potential abnormalities indicating lesions outside the clinically affected pathways were found in 0/5 patients with acute syndromes and in 3/18 of those with chronic syndromes. Thus MRI was more sensitive than BAEP and VEP combined in demonstrating the presence of clinically unsuspected lesions outside the spinal cord.

In the patients with an acute syndrome MRI revealed an area of abnormal signal intensity within the cervical cord in 5/7 patients, in 2 of whom the cord appeared swollen. In no patient with a clinically localized lesion of the thoracic cord did MRI demonstrate a lesion within the cord. Two patients with cord abnormalities demonstrated by MRI had no cerebral abnormalities visible. SEPs failed to demonstrate a lesion within the spinal cord in any of the patients with an acute syndrome.

In those patients with a chronic syndrome, 2 with clinical evidence of a lesion within the cervical spinal cord had abnormalities within the cord on MRI. In neither of these were SEPs recorded. The SEPs revealed a cord lesion in 1/5 patients who were examined with a cervical cord syndrome and in 3/13 in whom there was clinical evidence of a thoracic cord lesion.

Oligoclonal IgG bands were found in the CSF in 5/17 patients with chronic syndromes but in 0/9 with acute syndromes.

Spinal syndromes are a common mode of presentation of MS and it is likely that an appreciable proportion of patients with disseminated lesions at presentation have this disease. The probability is increased in those with oligoclonal bands in the CSF (Moulin *et al.*, 1983), but even these cases do not at presentation fulfil the criteria of the Poser Committee (Poser *et al.*, 1983). The implications of multiplicity of lesions at MRI are considered in the Discussion.

### *Comparison of MRI in MS and isolated lesions*

The distribution of the additional abnormalities seen in all three types of isolated lesion resembled that of MS. A quantitative comparison of the abnormality (calculated as for MS) showed that there were more abnormalities in known MS than in the patients presenting with clinically isolated lesions ( $P < 0.001$ ) although there was some overlap in that the lowest score in a patient with clinically definite MS was 9 and the highest score in a patient with an isolated syndrome was 42. There was no significant difference between the scores in the three groups of patients with isolated lesions.

### *Cerebral vascular disease*

Although cerebral vascular disease is infrequently confused with MS clinically, it may be when there is an acute onset, for example, of a hemiparesis or brainstem lesion. Moreover, the periventricular lucencies seen on x-ray CT scans in diffuse cerebral vascular disease (Rosenberg *et al.*, 1979; Goto *et al.*, 1981) and MS (Radue and Kendall, 1978, Hershey *et al.*, 1979) may be very difficult to distinguish, as may the small lucencies in the cerebrum seen in lacunar infarction and MS. In order to determine whether there are reliable features which can be used to separate some of these conditions we have studied the NMR images in 55 patients with a variety of syndromes attributable to cerebral vascular disease, and compared them with images obtained in MS. The ages of these patients with vascular disease ranged from 14 to 80 yrs (mean 50 yrs); 13 had late onset epilepsy associated with lacune-like abnormalities on CT scans in the white matter of the cerebral hemispheres; 11 had the clinical picture, confirmed on CT scanning, of cerebral infarction in the territory of a major vessel; 8 had Behçet's disease (according to the criteria of Haim and Gilhar, 1980); 6 had systemic lupus erythematosus (SLE) (as classified according to the American Rheumatism Association Revised Criteria, Tan *et al.*, 1982); 4 had other forms of vasculitis; 3 had the syndrome of transient global amnesia; 2 had intracerebral haemorrhage demonstrated by CT scanning; and 1 had venous infarction. Finally, 7 patients had progressive dementia with evidence on CT scans of diffuse white matter abnormality (Valentine *et al.*, 1980). The nosological status of this last condition is at present difficult to define. It is sometimes referred to as subacute arteriosclerotic encephalopathy or Binswanger's disease (Janota, 1981; Kinkel *et al.*, 1985). However, patients with this syndrome may also have evidence of lacune-like lesions on CT scans (Goto *et al.*, 1981),

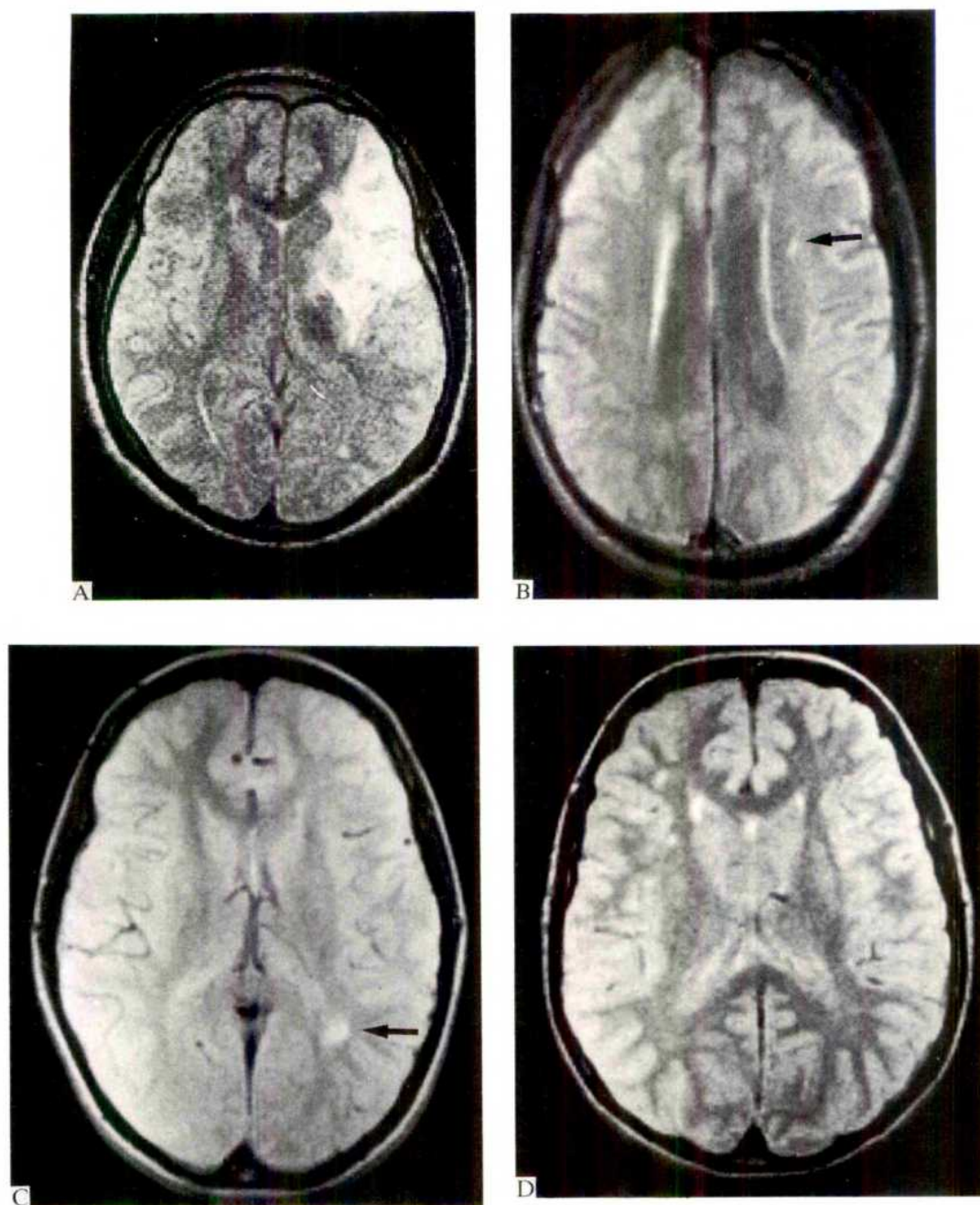


FIG. 13. Cerebral vascular disease. A, axial slice ( $SE_{2000/60}$  at 0.25 Tesla) of a 43-yr-old male with a left middle cerebral artery infarct. B, axial slice ( $SE_{2000/60}$ ) of a 65-yr-old male with episodes of vertebrobasilar ischaemia. There is smooth change along the body of the lateral ventricles and a discrete lesion in the left corona radiata (arrowed). C, axial slice ( $SE_{2000/60}$ ) of a 40-yr-old woman with Behçet's disease and transient episodes of vertigo and ataxia. There is a lesion at the left trigone (arrowed). D, axial slice ( $SE_{2000/60}$ ) of a 40-yr-old woman with established SLE who presented with an episode of confusion. There are several discrete lesions in the right frontal white matter.

raising the question of overlap with multi-infarct dementia (Hachinski, 1983). Since the pathogenesis of subacute arteriosclerotic encephalopathy is not established, although there is good evidence that the end result is infarction (Goto *et al.*, 1981; Janota, 1981), we have preferred to use the term 'dementia with diffuse white matter abnormality' suggested by Dr David Drachman (personal communication).

All 37 patients with noninflammatory (i.e., nonvasculitic) disease had previously undergone CT and abnormalities were found in 36. In no case were abnormalities seen on CT not visible also on MRI. MRI showed evidence of cerebral abnormalities in 10 patients who had shown no such abnormality on CT. Focal abnormalities were seen with MRI in all 37 and ranged in size from small lacune-like regions of altered signal to large lesions corresponding with the distribution of a major cerebral vessel in those with stroke (fig. 13A, B); 27 patients had evidence of periventricular abnormalities on the SE sequences (fig. 13B). Such abnormalities were seen in all patients with dementia with diffuse white matter abnormality and in 12/13 with lacune-like lesions.

Periventricular abnormalities were least common in patients with infarction in the territory of a fairly large cerebral vessel; the ages of the subjects in this group were lower with a mean age of 46 yrs (range 24–77 yrs). If the 3 patients in this group over the age of 60 yrs are excluded, none had periventricular areas of abnormal signal intensity.

Of 18 patients with inflammatory disease (i.e., Behçet's disease, SLE or another vasculitic disorder) 10 had periventricular changes and 8 had small discrete lesions in the cerebral hemispheres (fig. 13C, D). There were infarcts in the territory of a major cerebral artery in 2 patients, and 1 had small peripheral wedge-shaped lesions suggesting infarction.

It was important to try to distinguish the appearances of the periventricular abnormalities in cerebral vascular disease from those in MS. Of the 37 patients with such changes, 10 had a smooth line of increased signal around the bodies of the ventricles (fig. 13B) which differed from the irregular periventricular abnormalities found in 112/114 patients with MS. Smooth outlining of the ventricles was seen in all subgroups of patients with cerebral vascular disease except those with dementia with diffuse white matter abnormality. The remaining 27 cases showed irregularities in outline more or less resembling those seen in MS, although often the changes were milder. The changes reached an extreme degree in the 7 patients with dementia with diffuse white matter abnormality (fig. 14). In this group the changes resembled those seen in advanced MS although there was a tendency for the abnormalities in the latter to be more marked posteriorly and in the former to be evenly distributed. White matter changes extending into the centrum semiovale were seen in both conditions. Abnormalities were more frequently seen in the basal ganglia in patients with dementia with diffuse white matter abnormality than in those with MS ( $P < 0.001$ ). The differences in the distribution of abnormalities in other sites did not reach statistical significance although the number of patients with dementia with diffuse white matter abnormality was small.



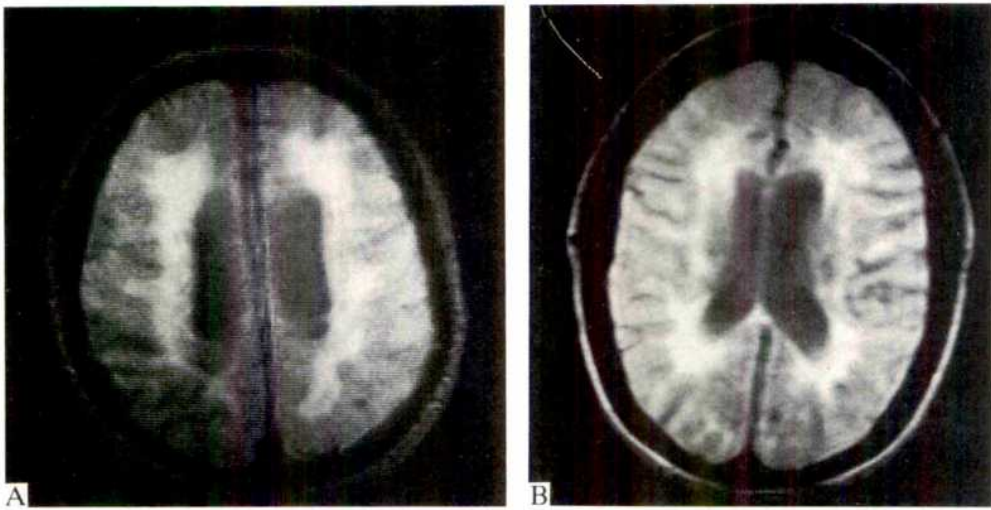


FIG. 14. Axial slices through the bodies of the lateral ventricles ( $SE_{2000/60}$ ). A, in a 58-yr-old male with long-standing hypertension and 4-yr history of progressive dementia and gait disturbance; B, in a 57-yr-old woman severely disabled with clinically definite MS.

In a further attempt to discriminate between the MRI abnormalities in dementia with diffuse white matter abnormality and those in MS, the relaxation times  $T_1$  and  $T_2$  were measured from computed images of abnormalities around the bodies of the lateral ventricles on each side and anteriorly and posteriorly (4 readings) using the computer reformatted images of relaxation times  $T_1$  and  $T_2$  (see Methods). The values obtained from the periventricular abnormalities taken from the patients in the former group were compared with those from 35 patients with MS. There was considerable overlap between the values obtained from the two groups and no statistically significant difference between them was found by analysis of variance.

It is thus clear that each of the individual features we have analysed which are seen in MS are also seen in cerebral vascular disease. Nevertheless, the pattern of MRI abnormalities was usually strongly suggestive of the correct diagnosis. Kortman *et al.* (1985) reached the same conclusion.

#### *Cerebellar degeneration*

An episode of unsteadiness of gait is not uncommon as the initial manifestation of MS. Progressive ataxia is less common but when it occurs in the absence of a family history it may be difficult to distinguish clinically from the cerebellar degenerations of middle life. We therefore undertook a study of MRI in this group of disorders, examining 12 cases with a recognizable genetic syndrome and 12 with idiopathic late onset cerebellar ataxia (Harding, 1984). The patients ranged in age from 24 to 64 yrs (mean 42 yrs).

Friedreich's ataxia is readily distinguished from MS by its clinical and electrophysiological features and autosomal recessive pattern of inheritance (Harding,



1984). Four patients were studied. In all there was brainstem atrophy and 1 also showed cerebellar atrophy. In none was there evidence of cortical atrophy.

The remaining 8 cases with inherited ataxic syndromes comprised 5 with autosomal dominant inheritance (Type 1 of Harding, 1982) and 3 with recessive disorders (1 with Kjellin's syndrome, 1 associated with spastic paraplegia and 1 with extrapyramidal features; *see* Harding, 1984). Cerebellar atrophy was present in all except the patient with Kjellin's syndrome. Brainstem atrophy was present in 4/5 dominantly inherited cases but in only 1 of recessive type. Cerebral cortical atrophy was seen in 3/5 with dominantly inherited syndromes and all of those with recessive syndromes.

Periventricular lesions were present in 2/3 with recessively inherited disease, 1/4 with Friedreich's ataxia, and 3/5 with autosomal dominantly inherited disease (fig. 15A). In all, the lesions differed from those seen in MS by being smooth in outline. No case with Friedreich's ataxia or other recessively inherited ataxia had discrete cerebral lesions, but 3/5 of those with a dominant syndrome did (fig. 15A).

Broadly similar findings were present in the sporadic cases of late onset cerebellar degeneration in none of whom was there clinical or investigative evidence of MS. Cerebellar atrophy was present in 10/12 compared with 7/12 of the 'definitely genetic' cases (fig. 15B). Brainstem atrophy was present in 6/12 (5/12 of the genetic cases). Cerebral cortical atrophy and smooth periventricular changes were rather less frequent: 2/12 compared with 6/12 of the genetic cases for each. Discrete

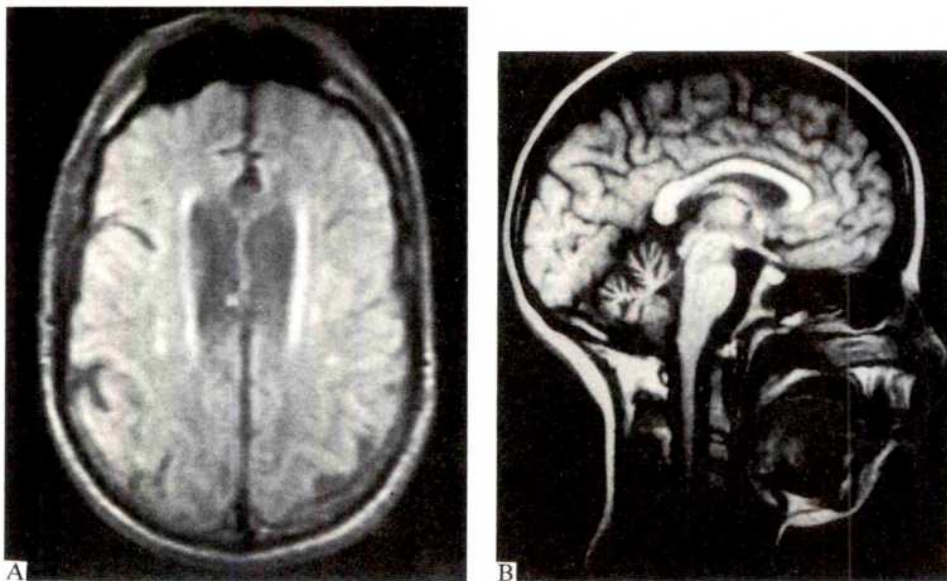


FIG. 15. A, axial slice (SE<sub>2000/60</sub>) from a 64-yr-old male with a dominantly inherited cerebellar degeneration. There are smooth periventricular changes and discrete lesions in the cerebral white matter. B, sagittal image (IR<sub>2000/500/40</sub>) showing marked cerebellar atrophy in a 22-yr-old female with a 7-yr history of progressive ataxia and a negative family history.

cerebral lesions were also less frequent: 1/12 sporadic compared with 3/12 in the genetic cases.

It was of particular interest to see whether the cases with regions of periventricular abnormality or discrete abnormalities in the cerebral white matter had other evidence that would raise the possibility of MS. Oligoclonal IgG bands in the CSF have not been described in cerebellar degeneration; they were tested for in 8 of the present series and found in none.

The numbers of cases in the individual subgroups of this series of patients is too small to permit characterization of the MRI changes in each of them. Considered as a whole however, the findings show important differences from patients with MS. The most clear-cut finding is that in the majority abnormalities were not seen in the periventricular region and when they were, the smoothness of outline differed from that seen in MS. Since periventricular changes are almost always present in MS it is reasonable to conclude that in patients with established progressive cerebellar ataxia, the absence of such changes, especially in a setting of cerebellar and/or brainstem atrophy, makes a diagnosis of MS highly unlikely.

The frequency and distribution of atrophy in this series of patients is in accord with the pathological description (reviewed by Oppenheimer, 1979; Harding, 1984). Periventricular and focal white matter lesions have not been described, and their significance remains to be determined.

#### *Other conditions*

Structural abnormalities in the region of the brainstem, foramen magnum and spinal cord not infrequently cause diagnostic difficulty in patients with progressive spasticity or ataxia in middle life. We have scanned 14 patients aged 17 to 65 yrs (mean 42 yrs) with Chiari types I and II malformations (8), brainstem glioma (2), spinal cord tumour (2), prepontine epidermoid (1) and cervical spondylitic myelopathy (1). Cerebellar ectopia, syringomyelia, and tumours of the brainstem and spinal cord were readily revealed (figs 16, 9A), although bony abnormalities per se were not because of the small number of water protons present in cortical bone. However, bony abnormalities of cancellous bone containing marrow were often obvious, as were protrusions of intervertebral discs.

We have had the opportunity to scan small numbers of patients with neurological manifestations of histologically proved sarcoidosis (7), chicken pox encephalitis (2) and metachromatic leucodystrophy (2). Our experience is insufficient to define the MRI characteristics of these conditions, but in the context of the present paper it is worth noting that in each group we have seen patients with periventricular changes and discrete cerebral abnormalities (fig. 17).

The findings in the 2 cases of chicken pox encephalitis are noteworthy. Both patients were scanned in the symptomatic phase and multiple cerebral white matter abnormalities were visible. A follow-up scan in one of these patients after 18 months showed the lesions persisting. The possibility thus arises that such appearances in

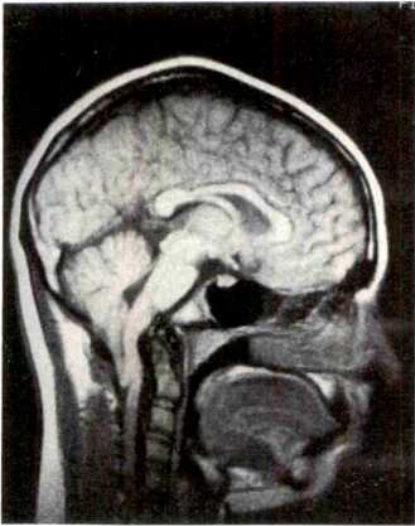


FIG. 16. Sagittal image ( $SE_{500/40}$ ) from a 15-yr-old female with ataxia and downbeat nystagmus. The cerebellar tonsils extend down to C2. The medulla is depressed and impressed.

apparently healthy individuals (*see below*) and in some patients with neurological disease may reflect past illness and be unrelated to the patient's present condition.

Because of our interest in the possibility that the MRI changes in chronic lesions reflect gliosis, we scanned 1 patient who had had a stereotactic prefrontal leucotomy 15 yrs previously (fig. 18A). Morphologically, the sites of leucotomy are characterized by the presence of cystic cavities, foci of nerve fibre loss, reactive gliosis and in cases examined shortly after the operation, extensive haemorrhage (Meyer



FIG. 17. Axial image ( $SE_{2000/60}$ ) in a 25-yr-old female with progressive dementia from metachromatic leucodystrophy.



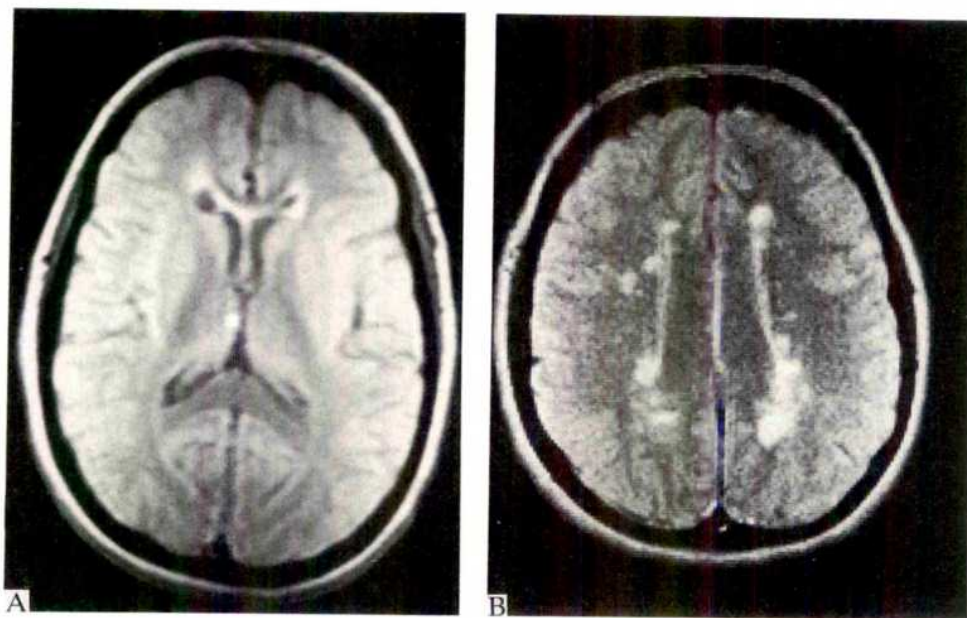


FIG. 18. A, axial image ( $SE_{2000,40}$ ) in a 40-yr-old female with a history of prefrontal leucotomy 15 yrs earlier. B, axial image ( $SE_{2000,60}$  at 0.25 Tesla) of a healthy control aged 50 yrs.

and Beck, 1945). The image in fig. 18A shows evidence of a cyst on one side and areas of increased signal on both. The spin-echo characteristics of the latter are indistinguishable from those of lesions in MS or cerebral vascular disease.

#### *Healthy controls*

When the present investigation began (April 1984), relatively little had been published about the findings in apparently healthy individuals. It was obviously important to establish the range of appearances encountered in 'normal' people of different ages using the sequences that were used to investigate patients with neurological disease. We scanned 53 men and women who believed themselves to be fit and in whom no evidence of past or present neurological disease was found on a general health questionnaire; they were not, however, examined neurologically. The ages ranged from 17 to 68 yrs (mean 46 yrs). In 48, no abnormalities were detected. In 2 of 3 individuals over the age of 60 yrs there was smooth altered signal in the periventricular region, as others have described (Brant-Zawadski *et al.*, 1985). In 2, aged 54 and 45 yrs, there were a few small areas of abnormality without periventricular changes. The origin of these changes is uncertain, but, as already mentioned, they could be a consequence of cerebral involvement in the childhood exanthemata or of occult vascular disease. One healthy individual showed extensive periventricular changes and discrete white matter abnormalities indistinguishable from those in MS (fig. 18B). We do not know whether this patient has MS or not, but the occasional finding of such abnormalities in normal individuals is in keeping

with the observations of Gilbert and Sadler (1983), who found evidence of 'unsuspected' MS at postmortem in 5 of 2450 brains examined at routine necropsy.

## DISCUSSION

This investigation has shown that characteristic periventricular and discrete abnormalities in the white matter were seen on NMR images in 99% of patients with clinically definite MS, which corresponded to the distribution of plaques at postmortem. Similar multiple MRI abnormalities were seen at presentation in between a half and two-thirds of patients with clinically isolated lesions of the kind seen in MS, such as optic neuritis, acute brainstem lesions and progressive spastic paraplegia. Although the changes in MS were not specific, more or less similar abnormalities being frequent in a variety of other conditions, their distribution was characteristic.

These observations provide a basis for assessing the role of MRI in the differential diagnosis of MS. Comparison of the images obtained in the different clinical groups showed that although no change was specific to any single disease process, the form and distribution of abnormalities could point strongly to particular diagnoses. The outline of the periventricular abnormalities was almost invariably irregular in MS, reflecting the finger-like extensions of the lesions (Dawson, 1916) along the cerebral veins (Fog, 1965) whereas, with the notable exception of dementia with diffuse white matter abnormalities, the periventricular changes in cerebral vascular disease and in ageing were sometimes smooth in outline, and often less extensive. Like Kortman *et al.* (1985), we found that discrete brainstem lesions were more common in MS than in cerebral vascular disease. This finding was, however, of little value on its own in the individual patient. Abnormalities conforming to the distribution of major cerebral vessels of course provided strong evidence of vascular disease.

It is clear that MRI is the most sensitive means currently available for detecting lesions in MS. The relative lack of specificity of the changes, however, limits the role of the technique at present to an anatomical one, namely that of determining whether multiple lesions are present. It is likely that with increasing experience, detailed analysis of the appearances and distribution of lesions will provide a useful contribution to differential diagnosis. Evoked potentials have a similar anatomical role, but sensitive though they are to defects in the pathways subserving them, they are less useful than MRI in establishing multiplicity of lesions because they sample such small fractions of the central white matter. In essence, the present contributions of MRI and evoked potentials to the assessment of patients suspected of having MS are similar: they can detect the presence of a lesion (provided it is greater than a certain minimum size) but the interpretation of its significance depends on the clinical context.

In patients scanned once at presentation with a single acute neurological episode (e.g., optic neuritis) the presence of multiple lesions cannot of itself be used as a

basis for the diagnosis of MS, even though the distribution of lesions may be highly suggestive. In high prevalence areas such as the United Kingdom it is of course likely that most patients with multiple lesions at presentation will subsequently develop clinically manifest dissemination of lesions, but at present the risk that an individual patient will do so is not established. The diagnosis of MS becomes clinically probable (Poser *et al.*, 1983) if subsequent scans reveal new lesions, provided that appropriate precautions to ensure precise repositioning of the head have been taken and the same sequences are used. The timing of subsequent scans is a matter for judgement, but in conformity with the criteria of Poser *et al.* (1983) they should not be used for diagnostic reassessment until at least one month has elapsed, and on the whole we recommend an interval of about six months to minimize the risk of misdiagnosing a case of rather slowly evolving encephalomyelitis as MS.

MRI is of particular value in certain kinds of patient. First, there are those in the less definite categories of MS. In the patient with a history of several episodes of neurological disturbance but with clinical evidence of only a single lesion, the finding of multiple lesions enables a clinically definite diagnosis to be made.

A second group of patients in which MRI is useful is that with progressive ataxic and spastic syndromes in middle life. Congenital anomalies, tumours and cysts in the region of the foramen magnum, spinal cord and brainstem are easily recognized. The finding of brainstem or cerebellar atrophy in patients with an established picture of progressive ataxia in the absence of abnormalities in the white matter provides strong evidence for a diagnosis of cerebellar degeneration and against a diagnosis of MS. The presence on a single scan of irregular periventricular changes and discrete lesions in the intracranial white matter is not sufficient to diagnose MS. As for acute isolated lesions, a clinically probable diagnosis on MRI evidence requires the demonstration of the development of new lesions by serial scanning, provided of course that there is no better explanation for them.

The results derived from a comparison of quantitative data on the relaxation times  $T_1$  and  $T_2$  in acute and chronic brainstem lesions encourage us to think that further development of this approach may permit the differentiation of such lesions in a single scan, thereby permitting earlier diagnosis. It is important to stress, however, that this work is in an early stage of development and that since the values for  $T_1$  and  $T_2$  are influenced by the characteristics of the individual scanner our data cannot be applied directly to the interpretation of data from other sources.

A notable feature of our investigation, as of others, was the frequency with which there were discrepancies between the clinical features and the location and number of lesions as detected by MRI in MS and the clinical syndromes attributable to 'isolated lesions'. This is what should be expected from a knowledge of the pathophysiology of the disease. The complex issues involved are discussed by McDonald (1986).

### *Origin of MRI abnormalities*

The study of postmortem brains provided convincing evidence that the abnormalities seen on MRI correspond with plaques. The question now arises as to the origin of the abnormal signals. Any explanation must account for the similarities between the abnormal images in MS, a predominantly demyelinating disease, and the various forms of cerebral vascular disease in which both axons and myelin are destroyed (Janota, 1981; Allen, 1984).

The signal intensity in proton NMR images depends upon many different factors of which proton density and the relaxation times,  $T_1$  and  $T_2$ , are usually the most important. Since the signal from normal brain is largely derived from water protons (Bottomley *et al.*, 1984), and since  $T_1$  and  $T_2$  are strongly influenced by the macromolecular environment of that water, image abnormalities will result from changes in both the quantity of tissue water and its macromolecular environment. There are a number of possible mechanisms for the observed signal changes. The effects of demyelination on image appearances are difficult to predict: both the constituent lipid protons of myelin, and the water associated with it are effectively invisible in NMR images due to their very short  $T_2$  relaxation times. It would be expected, therefore, that demyelination per se would have little effect on the image appearances. Following the loss of myelin, however, there remains a larger proportion of the tissue which may be occupied by water molecules of longer  $T_2$  relaxation times which are able to generate a detectable signal. Thus, it is possible that demyelination may lead to secondary changes in the tissue NMR parameters, and so to image intensity of white matter.

In the chronic lesion of MS (fig. 4) and in dementia with diffuse white matter abnormality, gliosis is as striking as the myelin loss (*see* fig. 2, McDonald, 1986). Electron microscopy shows that in the plaque of MS the space created by the disappearance of myelin is filled by the cytoplasm-rich fibrillary astrocytic processes; the appearance is well illustrated in fig. 4 of Prineas and Connell (1978). The expectation that these changes would result in an increase in water content per unit volume is supported by the measurements of Tourtellote and Parker (1968) who showed that there is a significant increase of water content in plaque tissue compared with normal white matter. It is therefore likely that the abnormalities in MR images to some extent reflect gliosis by virtue of the increase in water protons. It is also possible that differences between the macromolecular environment of water in astrocyte processes and in the normal tissue water spaces contribute.

The origin of the halo-like abnormalities seen in some patients is at present uncertain, and more than one mechanism may be involved. One possibility is that they represent lesions undergoing centrifugal enlargement with an outer rim of active myelin breakdown and a core of established gliosis and demyelination (*see* Prineas and Connell, 1978). Alternatively they might represent new lesions with active central myelin breakdown accompanied by oedema and cellular infiltration which progressively diminishes peripherally.

It is generally believed that water passes from the CSF into brain substance, particularly under conditions in which the balance between intraventricular pressure and brain compliance is disturbed. The contribution of this water, diffusing from the ventricle to the periventricular high signal area, might be substantial and find its way especially to neighbouring regions of damaged brain.

Data on the cerebral water content are not available for dementia with diffuse white matter abnormality or the lesion produced by leucotomy, but from the histological similarities it seems likely that the MRI abnormalities in these conditions have a similar origin. The observation that the gliosis following experimental vasogenic oedema in the cat is accompanied by similar MRI abnormalities suggests that gliosis is in part responsible for the abnormal MR images of a variety of affections of white matter (D. Barnes, W. I. McDonald, D. N. Landon, G. Johnson, unpublished observations).

The origin of the MRI abnormalities in the acute lesions of MS (e.g., in the brainstem) is probably more complex. Experimentally, both the acute vasogenic oedema of the lesion produced by cortical freezing and the cytotoxic oedema of acute triethyl tin intoxication are associated with striking MRI abnormalities (Barnes *et al.*, 1986, 1987). The two types of acute oedema can be distinguished from each other (reflecting their different protein content) and from the chronic (gliotic) cold lesion by the pattern of alterations in the measured value of  $T_1$  and  $T_2$ . Adams (1983) has described oedema in association with the acute lesions of MS and it seems likely that the MRI changes in such lesions reflect alterations in the quantity and distribution of tissue water. A relative increase in intracellular water per unit volume due to the accumulation of macrophages and the activation and proliferation of astrocytes might also play a part, though a smaller one.

It is of interest that serial imaging in experimental vasogenic oedema has shown that the acute image abnormalities disappear after about a week, coincident with the resolution of the oedema, only to become abnormal again after two to four months, corresponding with the development of gliosis (D. Barnes, W. I. McDonald, D. N. Landon, G. Johnson, unpublished observations). These observations have implications for the interpretation of MR images in MS. The failure to identify an abnormality after the acute development of a symptom may not mean that none was present earlier or that none will be obvious later; and the apparent disappearance of a lesion (spontaneously or during treatment) need not imply resolution of the pathological changes with restoration of normal structure. Serial studies in patients with acute lesions made at short intervals will be necessary to determine how important these considerations are in human disease.

Much of the white matter between the plaques in MS appears macroscopically normal both at postmortem and by MRI. Nevertheless we found quantitative differences in  $T_1$  and  $T_2$  between the normal-appearing white matter in MS and in healthy individuals. The explanation probably lies, at least in part, in the limited resolution of our MRI system with the scan times used (voxel size approximately  $30\text{ mm}^3$ ). Established plaques and oedematous regions smaller than this would not



be visible on the images but might change the values of  $T_1$  and  $T_2$ . It is also possible that changes in the density and macromolecular environment of protons caused by the diffuse increase in the number of astrocytes present in normal-appearing white matter in MS (Allen 1984), and the presence of myelin breakdown products in scattered microscopic lesions play a part. The quantitative data thus provides a more accurate reflection of the diffuseness of pathological changes in MS than the visual impression gained from the MR images or naked eye examination of the cut brain or stained sections. Both the natural history of the individual plaque and the background changes in the intervening white matter are of great interest in relation to the pathogenesis and pathophysiology of the disease. MRI offers the possibility of investigating the changes serially as resolution improves and quantification becomes more sophisticated.

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# CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

## A CLINICAL AND ELECTROPHYSIOLOGICAL STUDY OF 92 CASES

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### SUMMARY

Ninety-two patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been studied in order to define better the clinical features, course and prognosis of the condition and to identify possible aetiological factors. Sural nerve biopsy was performed on 87 subjects. Electrophysiological studies were undertaken on all patients and demonstrated marked slowing of motor conduction and impairment of sensory conduction. The onset was usually gradual but there was a rapid rate of onset in 15 (16%) patients. Males were more commonly affected than females. Weakness and paraesthesiae were the most common symptoms but pain was frequently a feature. Age of onset ranged from 2 to 72 years. Sixty patients (65%) had a relapsing course and 32 patients (35%) a progressive or monophasic course; there was a significantly earlier age of onset in patients with relapsing disease. Thirty-two patients (35%) gave a history of preceding infection or some other possible antecedent precipitating event and there was a significantly higher titre for cytomegalovirus antibodies in the serum of patients with CIDP than in controls. The patients were followed up for an average time of approximately ten years. Most patients (73%) had made a good recovery and were independent, but 7 patients had either died or were completely immobilized as a result of their disease. The value of treatment with corticosteroid therapy, immunosuppressive agents and plasma exchange is discussed.

### INTRODUCTION

The review of Austin (1958) focused attention on the condition of recurrent or relapsing neuropathy. Thomas *et al.* (1969) later described 5 patients with relapsing Guillain-Barré syndrome and drew attention to the similarities between their cases and those of Austin (1958). Many descriptive terms used to describe the illness reflected a lack of clear definition of the condition. These included relapsing corticosteroid dependent polyneuritis (Matthews *et al.*, 1970), steroid responsive recurrent polyneuropathy (DeVivo and Engel, 1970), relapsing hypertrophic neur-

itis (Dolman and Allan, 1973), subacute demyelinating polyneuropathy responding to corticosteroid treatment (Oh, 1978) and Guillain-Barré syndrome with slow progressive onset and persistent elevation of spinal fluid protein (Hinman and Magee, 1967). Dyck *et al.* (1975) introduced the term chronic inflammatory polyradiculoneuropathy (CIP) to include patients with progressive and chronic monophasic as well as relapsing courses and described the clinical features of 53 patients with this disorder. Later they used the term chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) to define the condition (Dyck *et al.*, 1982). A series of 23 patients with relapsing and chronic monophasic courses and pathological features of a demyelinating neuropathy was reported from our laboratory (Prineas and McLeod, 1976). Since that time the number of patients we have studied has increased to 92 and we now report our experience with this larger series in order to define better the clinical features, course and prognosis of CIDP and to identify possible aetiological factors.

## METHODS

### *Selection of patients*

All the patients were referred for investigation between 1968 and 1983 inclusive and satisfied the diagnostic criteria previously described (Dyck *et al.*, 1975; Prineas and McLeod, 1976; Dyck and Arnason, 1984). They had a demyelinating neuropathy with either a relapsing and remitting course or a subacute onset followed by steady progression or subsequent remission. For the purposes of this classification, a relapse was defined as a worsening of symptoms or signs, resulting in an increase in the disability by one or more grades on the disability scale with subsequent improvement (Prineas and McLeod, 1976; McCombe *et al.*, 1987). The histological criteria for demyelination were the presence in the nerve biopsy of demyelination affecting 15% or more of teased fibres or evidence of active demyelination and inflammatory infiltrates on electron microscopy or both; the electrophysiological criteria were motor nerve conduction velocities of less than  $40 \text{ m} \cdot \text{s}^{-1}$  in the median and ulnar nerves, or less than  $30 \text{ m} \cdot \text{s}^{-1}$  in the peroneal nerve, or terminal latency greater than 7 ms in the median or ulnar nerves or 10 ms in the peroneal nerve (McLeod *et al.*, 1973) or conduction block and/or differential dispersion of the compound muscle action potential (Lewis and Sumner, 1982). All patients had extensive investigations to exclude other causes of neuropathy (McLeod *et al.*, 1984). Patients with underlying carcinoma or associated paraproteinaemia were excluded from the study group.

### *Follow-up examinations*

Attempts were made to contact and reexamine patients during 1983–4. Sixty-seven patients were reviewed and their disability graded according to the criteria previously defined by Prineas and McLeod (1976): 0 = normal, 1 = signs but no symptoms or vice versa, 2 = mild motor and/or sensory symptoms with signs, 3 = moderately disabled by motor and sensory symptoms including ataxia, 4 = requiring assistance with eating or dressing, or using a walking aid, 5 = not ambulant, 6 = dead.

### *Viral serology*

Complement fixation titres of antibody to cytomegalovirus (CMV), Epstein-Barr (EB) virus, herpes simplex virus and varicella zoster were measured in the Department of Microbiology, Royal Prince Alfred Hospital, Sydney. IgG antibody to cytomegalovirus was measured in a group of patients by means of an enzyme immunoassay (Cytomegalisa Test Kit, MA Bioproducts). Patient and control sera were tested simultaneously. Absorbance of test sera was compared with a standard, and a score

derived for each sample. A score equal to or greater than 0.24 was regarded as positive and was equivalent to a complement fixation titre of 1:8 or greater.

#### *Sural nerve biopsy*

Sural nerve biopsies were performed and prepared for light and electron microscopic examination and morphometric studies using techniques previously described (Prineas and McLeod, 1976; McLeod *et al.*, 1984).

#### *Statistical methods*

Mean values were compared using the Student's unpaired *t* test. Values of  $P=0.05$  were regarded as significant. For comparison of disability scores, the trend  $\chi^2$  test was used.

## RESULTS

Ninety-two patients (57 males, 35 females) fulfilled the criteria for diagnosis of CIDP. Sural nerve biopsy was performed on 87 subjects. CSF protein levels in 72 patients on whom lumbar punctures were performed ranged from 0.23 to 5.50 g/l (mean 1.38, SD 1.11). The results of nerve conduction studies are shown in Table 1 and fig. 1.

TABLE 1. CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: NERVE CONDUCTION STUDIES

|                            | Motor conduction |                                  |                 |                                  |                 |                                  | Sensory conduction      |                         |
|----------------------------|------------------|----------------------------------|-----------------|----------------------------------|-----------------|----------------------------------|-------------------------|-------------------------|
|                            | Median           |                                  | Ulnar           |                                  | Common peroneal |                                  | Median                  | Ulnar                   |
|                            | Latency<br>(ms)  | Velocity<br>(m·s <sup>-1</sup> ) | Latency<br>(ms) | Velocity<br>(m·s <sup>-1</sup> ) | Latency<br>(ms) | Velocity<br>(m·s <sup>-1</sup> ) | Amplitude<br>( $\mu$ V) | Amplitude<br>( $\mu$ V) |
| <b>CIDP</b>                |                  |                                  |                 |                                  |                 |                                  |                         |                         |
| Mean $\pm$ SD              | 9.1 $\pm$ 6.0    | 30.4 $\pm$ 14.4                  | 6.8 $\pm$ 4.3   | 29.3 $\pm$ 13.1                  | 10.4 $\pm$ 4.6  | 29.5 $\pm$ 10.9                  | 2.3 $\pm$ 4.4           | 1.6 $\pm$ 3.2           |
| Range                      | 2.6–14.0         | 9–62                             | 2.8–25          | 8–54                             | 2.5–23          | 9–50                             | 0–20                    | 0–17                    |
| n                          | 73               | 77                               | 62              | 67                               | 48              | 48                               | 75                      | 69                      |
| <b>Controls</b>            |                  |                                  |                 |                                  |                 |                                  |                         |                         |
| Mean $\pm$ SD              | 3.4 $\pm$ 0.5    | 56.9 $\pm$ 5.0                   | 2.1 $\pm$ 0.4   | 55.7 $\pm$ 4.6                   | 4.6 $\pm$ 1.0   | 47.3 $\pm$ 4.9                   | 17.9 $\pm$ 7.5          | 13.7 $\pm$ 6.4          |
| Range                      | 2.5–4.9          | 49–66                            | 2.1–3.7         | 47–69                            | 3.3–7.7         | 38–55                            | 9–40                    | 5–36                    |
| n                          | 35               | 35                               | 35              | 35                               | 35              | 35                               | 35                      | 35                      |
| Significance of difference | $P < 0.001$      | $P < 0.001$                      | $P < 0.001$     | $P < 0.001$                      | $P < 0.001$     | $P < 0.001$                      | $P < 0.001$             | $P < 0.001$             |

### *Clinical features*

#### *Symptoms and signs at presentation*

Most patients (72%) presented with a sensorimotor neuropathy; 22% of patients had a predominantly motor neuropathy and 6% of patients had a sensory neuropathy. Weakness was present in 94% of patients and ranged from mild weakness of the intrinsic muscles of the hands and feet to severe weakness requiring ventilatory support. Paraesthesiae were reported in 64% of patients and were frequently the

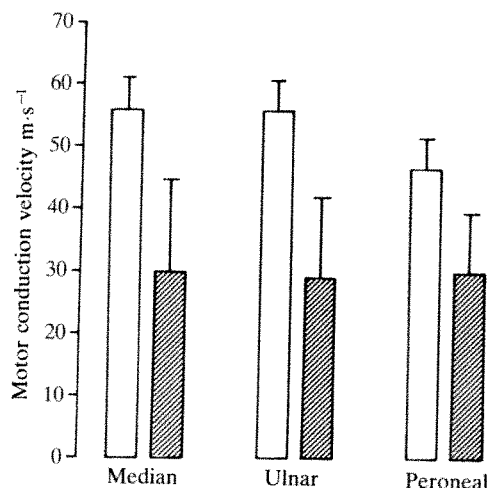


FIG. 1. Mean motor conduction velocities in median, ulnar, and common peroneal nerves in control subjects (open bars) and CIDP patients (hatched bars). Mean values are shown with 1 SD.

presenting symptom when weakness was mild. Pain was a symptom in 20% of patients in whom it was usually the chief complaint and ranged from a sensation of burning feet to an aching pain in the muscles. Seventy-two per cent of patients had clinical evidence of sensory impairment that ranged from increased two-point discrimination to severe loss of all modalities. Cranial nerve involvement was found in 16% of patients; ophthalmoplegia was present in 4 patients (4%), facial weakness in 14 (15%) and bulbar weakness in 6 (6%). Papilloedema was present in 1 patient whose CSF protein level was 2.2 g/l. Tremor was observed in 3 patients. Autonomic dysfunction was not a feature of the condition; no significant abnormalities were found in 14 patients in whom autonomic function studies were performed.

### *Clinical course*

The patients were classified into two major subgroups, relapsing and nonrelapsing, according to their clinical course. The relapsing group consisted of 60 patients in whom there was a history of definite relapses and remissions. The nonrelapsing group consisted of 32 patients in whom there were no relapses and who had either a subacute onset of a monophasic type of illness or a clinical course that was chronically progressive.

The age of onset for the whole group of 92 patients ranged from 2 to 72 (mean 35.4, SD 20.3) yrs. There was no significant difference between the age of onset for males and females. Age of onset for patients in the relapsing group ranged from 2 to 70 (mean 26.8, SD 16.0) yrs and for the nonrelapsing group from 2 to 72 (mean 51.4, SD 17.7) yrs. The difference is significant ( $P < 0.005$ ) (Table 2, fig. 2).

In 15 patients (16%) there was a rapid rate of onset of the neuropathy, the plateau of disability being reached within a period of four weeks. However these patients were distinguished from those with the Guillain-Barré syndrome (GBS)



TABLE 2. CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: AGE OF ONSET

|              | <i>Mean</i> | <i>SD</i> | <i>n</i> | <i>Range</i> | <i>Median</i> |
|--------------|-------------|-----------|----------|--------------|---------------|
| Total group  | 35.4        | 20.3      | 92       | 2-72         | 33            |
| Males        | 37.1        | 19.4      | 57       | 2-71         | 39            |
| Females      | 32.6        | 21.6      | 35       | 2-72         | 25            |
| Relapsing    | 26.8        | 16.0      | 60       | 2-70         | 26            |
| Nonrelapsing | 51.4        | 17.7      | 32       | 2-72         | 56            |

by their subsequent relapsing or progressive course. The age of onset in this group ranged from 3 to 70 yrs (mean 22; SD 15). In the remaining 77 patients (84%) there was a subacute onset of symptoms.

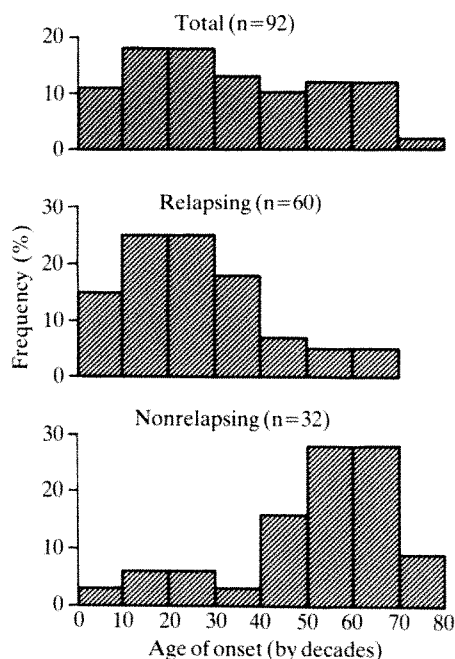


FIG. 2. Frequency distribution of age of onset of symptoms in patients with CIDP.

### *Onset in childhood*

There were 10 patients (5 males, 5 females) in whom the age of onset ranged from 2 to 10 yrs. In 7 patients there was a subacute and in 3 an acute onset of the disease. Eight patients have been followed up, 7 of whom had no disability and 1 had only minor disability. Three of the patients had experienced relapses in adult life.

*Associated diseases*

Nine patients had associated diseases with possible allergic or autoimmune aetiology. These were thyrotoxicosis (4), psoriasis (2), urticaria (1), iritis (1) and eczema (1). The patients with thyrotoxicosis had been diagnosed and treated before the onset of the neuropathy and all were euthyroid at the time of diagnosis of CIDP.

*Precipitating factors*

*History of preceding infection.* Twenty-nine patients (32%) gave a history of an illness in the six weeks preceding the onset of neuropathy (Table 3). In 21 patients

TABLE 3. CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: PRECIPITATING FACTORS

| <i>Illness</i>         | <i>No. of subjects</i> |
|------------------------|------------------------|
| Upper respiratory      | 18                     |
| Gastroenteritis        | 2                      |
| Cystitis               | 1                      |
| Smallpox vaccination   | 1                      |
| Salk polio vaccination | 2                      |
| Measles infection      | 1                      |
| Varicella infection    | 2                      |
| Mumps infection        | 1                      |
| Tetanus vaccination*   | 1                      |

(\* Pollard and Selby, 1978)

there were nonspecific upper respiratory, gastrointestinal or bladder infections and in 8 patients the onset of neuropathy was preceded by specific infections or vaccinations. Complement fixation viral titres were performed on fresh serum of 15 patients. Ten patients (67%) were found to have positive CMV titres ( $>1:4$ ) but there was no significant elevation of titres for EB virus, herpes simplex or varicella. Because of the high frequency of positive CMV titres, an enzyme immunoassay for cytomegalovirus was performed on the sera of 25 control subjects, 39 CIDP and 22 GBS patients (Table 4). Control subjects were laboratory workers and medical students, and patients were selected because of their geographic location and availability for study. The results on CIDP patients were identical to those obtained with the complement fixation test. The mean titre and the percentage of patients with a positive CMV titre were significantly greater for the CIDP patients than the control subjects. There was no significant difference in the scores of CIDP patients in relapse (mean 0.25, SD 0.14) when compared with those in remission (mean 0.24, SD 0.15) ( $P>0.05$ ). The mean score of patients receiving corticosteroids (mean 0.27, SD 0.17) did not differ significantly from those not receiving steroids (mean 0.24, SD 0.14) ( $P>0.05$ ). There was no correlation of the score on the CMV immunoassay with age.

*Pregnancy.* There were 16 women of childbearing age, 9 of whom became

TABLE 4. RESULTS OF ENZYME IMMUNOASSAY FOR CYTOMEGALOVIRUS IN CIDP, GBS, AND CONTROL SUBJECTS

|                                 | <i>Controls</i> | <i>GBS patients</i> | <i>CIDP patients</i> |
|---------------------------------|-----------------|---------------------|----------------------|
| No. of subjects                 | 25              | 22                  | 39                   |
| Age of subjects (yrs)           |                 |                     |                      |
| Mean age                        | 29              | 36                  | 44                   |
| SD                              | 5               | 19                  | 20                   |
| Range                           | 23-45           | 14-68               | 3-73                 |
| Cytomegalovirus test scores†    |                 |                     |                      |
| Mean score                      | 0.10            | 0.24*               | 0.25*                |
| SD                              | 0.08            | 0.13                | 0.15                 |
| Percentage with positive scores | 8%              | 50%                 | 48%                  |

\*  $P < 0.001$ . †  $\geq 0.24$  is positive.

pregnant. In 4 of these women onset occurred in pregnancy and in the other 5 there were relapses related to pregnancy. There was a significant increase in the number of relapses during the pregnancy and three months postpartum and a tendency for symptoms to worsen during the third trimester or immediate postpartum period. The analysis of the association with pregnancy has been reported elsewhere (McCombe *et al.*, 1987).

#### *Response to treatment*

Seventy-six patients were treated with corticosteroids. In 49 patients (65%) there was improvement ranging from increased functional ability to complete remission. In some patients continued corticosteroid therapy was required since relapses occurred when the steroids were withdrawn. Twelve patients received no benefit from steroids and were treated with immunosuppressive drugs. Seven patients received azathioprine with improvement in 4 cases, and 4 of 5 patients treated with cyclophosphamide improved.

Plasma exchange was performed on 13 patients (Pollard *et al.*, 1983, 1985). Eight patients (61%) improved and 2 required regular exchanges ranging from weekly to third weekly to maintain initial benefit.

#### *Disability at follow-up*

Seventy-six patients were alive and available for follow-up and 5 patients had died as a result of their disease. The interval of time from onset of the disease to final review or death was 1 to 41 yrs (mean 10.6, SD 9.1). Six patients were lost to follow-up and 5 others had died as a result of intercurrent illnesses, unrelated to CIDP. Most patients (73%) had made a good recovery and were independent with a disability of 2 or less but 2 patients (2%) were grade 5 on the disability scale because of inability to walk and severe muscle wasting and 5 patients (6%) had died as a result of their disease (fig. 3, Table 5).

The disability of the patients with relapsing disease was compared with that of patients with the nonrelapsing type. Patients with the relapsing disease were

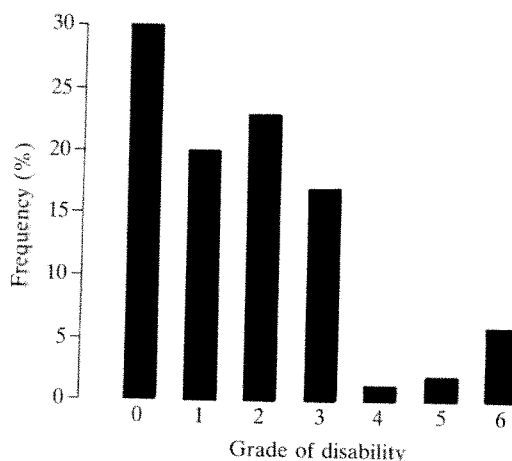


FIG. 3. Frequency distribution of grade of disability at follow-up in 81 patients with CIDP.

TABLE 5. CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: DISABILITY AT FOLLOW-UP

|                                             | Total    | Relapsing | Nonrelapsing |
|---------------------------------------------|----------|-----------|--------------|
| Disability grade (Prineas and McLeod, 1976) |          |           |              |
| 0                                           | 24 (30%) | 19 (36%)  | 5 (17%)      |
| 1                                           | 16 (20%) | 11 (21%)  | 5 (17%)      |
| 2                                           | 19 (23%) | 10 (19%)  | 9 (31%)      |
| 3                                           | 14 (17%) | 7 (13%)   | 7 (24%)      |
| 4                                           | 1 (1%)   | 0         | 1 (3%)       |
| 5                                           | 2 (2%)   | 2 (2%)    | 0            |
| 6 Died of CIDP                              | 5 (6%)   | 3 (6%)    | 2 (7%)       |
| Other patients                              |          |           |              |
| Died of other causes                        | 5        | 2         | 3            |
| Lost to follow-up                           | 6        | 6         | 0            |

reviewed after 1 to 41 yrs of illness (mean 12.8; SD 9.6,  $n=52$ ). Fifty-seven per cent of patients had grade 0 or 1 disability and the median disability score was 1. Patients with the nonrelapsing type of disease were reviewed at 1 to 22 yrs (mean, 6.5, SD, 6.4;  $n=29$ ) after the onset of their illness; 34% of patients had grade 0 or 1 disability and the median disability score was 2. The differences are not significant (Trend  $\chi^2 = 3.3$ ,  $0.1 > P > 0.05$ ). When the nonrelapsing group was further analysed, the median score for patients with chronic/progressive disorder was 3 and that for the patients with the subacute remitting disorder was 1.

## DISCUSSION

All patients fulfilled the criteria for diagnosis of CIDP (Dyck *et al.*, 1975; Prineas and McLeod, 1976; Dalakas and Engel, 1981; Sumner, 1984; Dyck and Arnason, 1984). They had a predominantly symmetric sensorimotor neuropathy with either

a relapsing course or a chronic monophasic or steadily progressive course, without the presence of an associated causal disease. There was electrophysiological or histopathological evidence, or both, of peripheral nerve demyelination and commonly an elevated CSF protein. The histopathological findings in the sural nerve did not differ from those described in detail in our earlier report (Prineas and McLeod, 1976). Other laboratory investigations were normal; patients with paraproteinaemia were excluded from the present analysis.

We have classified our cases into relapsing and nonrelapsing groups using criteria similar to those described by others (Thomas *et al.*, 1969; Prineas and McLeod, 1976; Dalakas and Engel, 1981; Schaumburg *et al.*, 1983). Patients who had definite relapses but without complete recovery are included in the relapsing group; some of these may fall into the stepwise progressive category described by Dyck *et al.* (1975). We did not include in this group patients whose relapses were related only to reduction or cessation of steroids or immunosuppressive therapy. Cases with a steadily progressive course, and those with a subacute onset and monophasic course, have been included in the nonrelapsing group. The difficulties in classifying precisely the course of the illness in some cases has been previously emphasized (Schaumburg *et al.*, 1983). Cases of typical GBS in whom a single relapse occurred with a time course similar to the original episode were defined as recurrent GBS and not included in the present study (Dyck and Arnason, 1984), but cases that commenced with an acute onset and then developed a chronic course or had multiple relapses were included.

Sixty patients (65%) had a relapsing course and 32 (35%) nonrelapsing, proportions similar to those in our earlier study (Prineas and McLeod, 1976). In the series of Dyck and coworkers (Dyck *et al.*, 1975; Dyck and Arnason, 1984) there were 34% of patients with a relapsing course and a further 34% of patients who had a stepwise progressive course. If these two categories together are considered to be the same as our relapsing group and their gradually progressive (15%) and monophasic (15%) categories similar to our nonrelapsing group, then the two series are very similar in their composition.

In our present series there was a predominance of male patients (62%) a finding that is in accordance with that of other studies (Austin, 1958; Dyck *et al.*, 1975; Prineas and McLeod, 1976; Oh, 1978; Sladky *et al.*, 1986). As in other series all age groups were affected by the disease (Dyck *et al.*, 1975; Prineas and McLeod, 1976; Dalakas and Engel, 1981), but there was a significantly earlier age of onset in patients with the relapsing condition. Early age of onset has been also reported in other studies of patients with relapsing neuropathy; the average age of onset in Austin's (1958) series was 23 yrs and 26 yrs in that of Thomas *et al.* (1969).

The clinical features did not differ substantially from those reported previously (Dyck *et al.*, 1975; Prineas and McLeod, 1976). Weakness of proximal and distal muscles, and paraesthesiae are the most common symptoms and reflexes are usually depressed or absent. Pain was a dominant symptom in 20% of patients, a frequency similar to that of 15% and 17% in hands and feet respectively reported by Dyck

*et al.* (1975). The cranial nerves were involved in 16% of patients, a frequency similar to that in other series (Dyck *et al.*, 1975; Dalakas and Engel, 1981). One patient (1%) had papilloedema, a somewhat lower incidence than that of 7% in the study of Dyck *et al.* The mechanism of papilloedema is unknown but is occasionally seen in the GBS also and may be related to raised intracranial pressure or an elevated CSF protein (Morley and Reynolds, 1966; Sullivan and Reeves, 1977). Three patients (3%) had an action tremor; intention tremor (Thomas *et al.*, 1969), ataxic tremor (Prineas and McLeod, 1976) and postural and action tremor (Dalakas and Engel, 1981) have been previously reported, but the mechanism is uncertain (Dalakas *et al.*, 1984).

Most patients (72%) presented with a sensorimotor neuropathy; 22% of cases had a predominantly motor neuropathy and 6% of cases had a predominantly sensory neuropathy. These findings are similar to those of others (Dyck *et al.*, 1975; Prineas and McLeod, 1976; Dalakas and Engel, 1981).

Twenty-nine patients (32%) gave a history of an illness or vaccination in the six weeks preceding the onset of neuropathy. This is higher than the proportion of 14/54 (24%) reported in the literature reviewed by Oh (1978). Dyck and Arnason (1984) found that 10/57 (19%) of their patients experienced antecedent events within the three months preceding the onset or exacerbation of the illness (7 received foreign protein, 3 had upper respiratory tract infections). They concluded that it was uncertain whether the incidence of antecedent infections exceeded that of the general population but it is considerably less than that in the GBS, in which approximately two-thirds of patients give a history of an antecedent acute infectious illness (Arnason, 1984). Our finding that there was serological evidence of previous CMV infection in a significantly higher proportion of patients with both CIDP and GBS than in the control population provides some evidence for an increased incidence of preceding infection in CIDP. Cytomegalovirus infection has previously been associated with attacks of GBS (Dowling and Cook, 1981).

Ten patients had an acute or subacute onset of neuropathy in childhood, 3 of whom had subsequent relapses in adult life. The 8 patients whom we were able to follow up had little or no disability. Our findings are consistent with those of others that CIDP in childhood may have an acute, subacute or insidious onset with a relapsing or progressive course; it is commonly steroid responsive (Colan *et al.*, 1980; Sladky *et al.*, 1986).

At follow-up, most patients (73%) were not seriously incapacitated by their illness, having a disability of 2 or less. However, 5 patients had died of the disease and 2 were quadriplegic and totally dependent. Dyck *et al.* (1975) found that 60% of patients were ambulatory and working with minimal disability, 28% were confined to bed or a wheelchair and 16% had died of the disease. The better outcome in our patients may reflect improved treatment in recent years with plasma exchange and immunosuppressive drugs. Patients with a relapsing course tended to have a more favourable prognosis than those with a nonrelapsing course, but the differences in disability at follow-up did not reach significant levels.

Forty-nine of 76 patients (65%) in the present study treated with corticosteroids improved. The efficacy of corticosteroid therapy has been reported by many previous workers (Austin, 1958; Thomas *et al.*, 1969; Matthews *et al.*, 1970; DeVivo and Engel, 1970; Dalakas and Engel, 1981; Oh, 1978; Prineas and McLeod, 1976; Dolman and Allan, 1973; Sladky *et al.*, 1986; Gabreëls-Feston *et al.*, 1986). Dyck *et al.* (1982) demonstrated in a controlled clinical trial that corticosteroid therapy resulted in a small but significant improvement compared with no treatment in both relapsing and progressive cases. Small numbers of our patients who were unresponsive to steroid therapy appeared to benefit from azathioprine and cyclophosphamide. Most reports of the use of these agents have also been on small numbers of patients and the value of the treatment remains unproven (Palmer, 1966; Yuill *et al.*, 1970; Walker, 1979; Pentland, 1980; Dalakas and Engel, 1981; Rosen and Vastola, 1976). One controlled trial showed no better results from treatment with combined prednisone and azathioprine than with prednisone alone (Dyck *et al.*, 1985). We have also treated patients who did not respond satisfactorily to corticosteroid therapy with plasma exchange. Eight of 13 patients (61%) improved and our finding that some, but not all, patients respond to this treatment is consistent with the observations of others (Levy *et al.*, 1979; Server *et al.*, 1979; Cook *et al.*, 1980; Gross and Thomas, 1981; Toyka *et al.*, 1982; Dyck *et al.*, 1986). The complication rate with plasma exchange using albumin replacement is so low in our experience that we use this therapy in preference to corticosteroids in some patients, particularly those requiring only short courses of plasmapheresis or only infrequent exchange. Patients with relapsing disease may need only a small number of exchanges, whereas in chronic progressive cases, exchanges at regular intervals over long periods of time may be required to maintain benefit. In patients in whom frequent exchanges are necessary, concomitant immunosuppressive therapy may help to reduce their frequency (Toyka *et al.*, 1982). Although the role of plasma exchange in CIDP has been established in a controlled study (Dyck *et al.*, 1986), there are no such studies of combined immunosuppression and plasma exchange. Until the pathogenesis of CIDP is better understood or unambiguous evidence of autoantibody provided, it would seem better to reserve immunosuppression for patients who fail to respond to corticosteroids or to plasma exchange alone, or who need frequent exchanges.

The similarities between CIDP and multiple sclerosis, chronic demyelinating diseases of the peripheral and central nervous systems respectively, have been previously noted (Prineas, 1970; Dyck and Arnason, 1984). In both diseases immunological mechanisms are probably implicated in the pathogenesis and responsible aetiological factors include a genetically determined predisposition to the disease (Stewart *et al.*, 1978; Adams *et al.*, 1979; McCombe *et al.*, 1985) and precipitating viral infections. The present study has also demonstrated that patients with a relapsing course have an earlier onset than those with a nonrelapsing course, a finding similar to that in multiple sclerosis (Confavreux *et al.*, 1980).

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## RETROSPLLENIAL AMNESIA

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### SUMMARY

A 39-year-old man developed retrograde and anterograde amnesia following haemorrhage from an arteriovenous malformation situated near the splenium of the corpus callosum. MRI studies demonstrated damage to the splenium, and to a region containing the retrosplenial cortex and the cingulate bundle. The fornix was anterior and inferior to the site of maximal damage, but may have been involved; the stria terminalis was probably spared. Structures known to be important in memory but spared by the lesion included the hippocampus, thalamus, and basal forebrain. The retrosplenial cortex receives input from the subiculum and projects to the anterior thalamus, thus providing an alternative route between hippocampus and thalamus. Perhaps more importantly, medial temporal structures involved in memory receive anterior thalamic input directly via the cingulate bundle and indirectly through a relay in the retrosplenial cortex. We suggest that this thalamocortical portion of Papez' circuit may be important in memory, and that lesions of the cingulum and retrosplenial cortex may cause amnesia by disrupting this pathway.

### INTRODUCTION

In 1977, Heilman and Sybert described a patient who developed severe amnesia in association with the growth and removal of a pilocytic astrocytoma near the trigone of the lateral ventricles. These authors postulated that the memory disturbance was caused by involvement of the fornix bilaterally. They recognized that fornix lesions in humans had not consistently been associated with amnesia; however, they argued that, first, cases of alleged normal memory following fornix transection were not well studied neuropsychologically and, secondly, lesions of the posterior fornix interrupt connections between the fornix and thalamus that would be spared by lesions of the columns of the fornix. Authors arguing against the importance of the fornix in memory have discounted Heilman and Sybert's evidence on the grounds that only surgical observation was available to document the extent of the lesion, and that other structures, such as the temporal stem or the posterior hippocampus, might have been involved by the tumour or by surgery (Horel, 1978).

We now report a patient with amnesia associated with haemorrhage from an

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arteriovenous malformation located between the splenium of the corpus callosum and the trigone of the left lateral ventricle. For convenience, we have referred to this area as the retrosplinal region, although the actual retrosplinal cortex is only one of the structures in this region. Neuroradiological studies in our case demonstrate no lesions in the hippocampus, temporal stem, or stria terminalis, and it is possible that the lesion did not involve the fornix. It unquestionably destroyed the cingulate bundle and retrosplinal cortex, structures that were also involved in the case reported by Heilman and Sybert. These two structures have strong anatomical connections with structures known to be important in memory, raising the possibility that lesions restricted to the retrosplinal area can be associated with amnesia.

### CASE REPORT

On March 15, 1984, T.R., a 39-year-old right-handed college-educated accountant, awoke with a severe headache. He was confused, and pyrexial, with a stiff neck and decreased memory. Lumbar puncture yielded blood-stained CSF. He was transferred to the Shands Teaching Hospital, University of Florida. His past medical history and family history were noncontributory. Nine months before the onset of his illness he had moved from California to a responsible post in the offices of a large corporation in Florida.

On admission (March, 15) his temperature was 38° C, and his blood pressure 118/90 mmHg. He had moderate meningism, was somnolent and orientated only for person. He recalled only 1 of 3 objects in 5 min, and had difficulty performing the serial 7s test. Spontaneous speech, comprehension and repetition were normal. He had a right homonymous hemianopia, full extraocular movements and normal pupillary responses. The rest of the cranial nerves were normal. He had no abnormal motor signs or alteration in reflexes and pain sensation was intact.

Urine and blood studies, including clotting studies, were normal. A CT scan showed blood in the ventricular system and an intracerebral haemorrhage just lateral to the splenium on the left (fig. 1). An angiogram showed an arteriovenous malformation (AVM) both above and below the splenium in the pericallosal cistern and the cistern of the velum interpositum, extending into the medial aspect of the trigone of the left lateral ventricle (fig. 2). Feeding vessels arose from interhemispheric branches of the left anterior and posterior cerebral arteries, and from choroidal branches of the left posterolateral choroidal artery. He was treated with dexamethasone, cimetidine, phenytoin and analgesics. He slowly became more alert. Repeat CT scans on March 21 and 29 demonstrated disappearance of the intraventricular blood and partial resolution of the intracerebral haemorrhage. There was slight ventricular enlargement.

Fifteen days after admission, he was alert and cooperative. He was orientated for place, person and year, but was unsure of the month. He remembered 1 of 3 objects after distraction, but did not recall the other 2 even with multiple choice. He had no recollection of the events of his illness, and he was very uncertain about time relationships before his illness; for example, he could not remember if he had moved to Florida before or after Christmas. Spontaneous speech was fluent, without errors, and repetition and naming were normal. He made occasional errors on calculations, but right-left orientation and finger naming were normal.

He had signs of a mild callosal disconnection. Although he made only occasional errors reading aloud and reading comprehension for short commands was normal, he sometimes failed to read correctly items in his left visual field. His writing was normal with his right hand; he made occasional errors with his left hand, but could type correctly with the left hand the same sentences that he had difficulty writing. He had some difficulty drawing with the left hand, but he was not apraxic with either hand.



FIG. 1. Axial CT scan taken on the day after the haemorrhage demonstrating an intracerebral haemorrhage medial to the trigone of the left lateral ventricle, with extravasation into the ventricle.

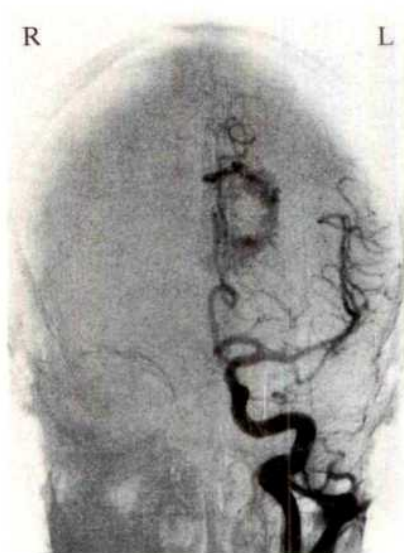


FIG. 2. Anteroposterior subtraction view of a left carotid angiogram, demonstrating the arteriovenous malformation arising from posterior branches of the anterior cerebral artery.

Visuospatial abilities were intact. With his right hand, he could draw a cube and a rudimentary map of Florida, and could correctly indicate the location of major cities. He performed the cancellation task normally with either hand. He had a partial right superior quadrantanopia to confrontation, and variable left visual field extinction on bilateral simultaneous stimulation. He could accurately count fingers on either side, and he could name colours in either visual field. Extraocular movements and optokinetic nystagmus were normal, as was the remainder of his neurological examination.

On April 5 the AVM was removed through a left occipitoparietal craniotomy. After several bridging veins along the interhemispheric fissure were divided, the left occipital lobe was retracted laterally, exposing the splenium. The posterior pericallosal artery was followed to the AVM, which was surrounded by an old haematoma. Using microdissection techniques the AVM was removed. The fornix was not directly visualized during the operation.

He remained somnolent postoperatively. A CT scan showed intraventricular blood with increased ventricular size. On April 6 ventriculostomy was performed. Three days later he was still somnolent, but could name objects placed in his left hand and was not apraxic. He then became unresponsive. The ventriculostomy continued to drain blood-stained CSF. He was treated for suspected meningitis, although only one CSF culture was positive (anaerobic streptococcus). He gradually improved, and by April 23 he was alert, but had a more extensive retrograde amnesia than preoperatively. He was discharged on April 28. On June 15, formal visual field testing demonstrated a partial right superior homonymous quadrantanopia. Eleven months after his haemorrhage he tried returning to work on a limited basis, but he was unable to perform his previous work because of memory limitations. Although improving, he has significant memory deficits 2 yrs after his haemorrhage.

*Neuropsychological testing*

Formal neuropsychological testing was performed preoperatively, and several times during the next 20 months (April 24, 1984; June, July, and October, 1984; November, 1985; January, 1986). Details of the most comprehensive testing are given in the Appendix. We will first consider testing performed preoperatively and within 4 months of surgery. During preoperative and early postoperative testing, he was alert, attentive, and socially appropriate. With the exception of an increase in the span of his retrograde amnesia from 9 months preoperatively to 4 yrs postoperatively, differences between preoperative and early postoperative testing were minimal.

On the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981), his verbal IQ was 118 preoperatively and 115 postoperatively; his memory quotient of 84 preoperatively was significantly reduced compared with his verbal IQ. All language and language-related functions were intact, as was performance on tasks associated with frontal-subcortical functions (i.e., Verbal Fluency (Benton, 1968; Lezak, 1976), Proverb Interpretations, Stroop, Visual-Verbal Test (Siegel, 1957)). The single exception was poor performance on the Wisconsin Card Sorting test (Milner, 1963; Robinson *et al.*, 1980): abnormal preoperative performance on this test was thought at the time to reflect difficulty in remembering the categories that he was sorting.

In contrast to these preserved functions, he had a profound amnesia. Retrograde amnesia was present at the onset of his illness. He could recall none of the events surrounding his illness, and he thought he still worked in another state. His retrograde amnesia transiently increased postoperatively to encompass more than 4 yrs: he did not remember the birth of his second child (aged 4 yrs), believing he had only one child. His remote memory, however, appeared intact, as assessed by the Albert Remote Memory Battery (Albert *et al.*, 1979). At 6 months postoperatively, his retrograde amnesia had shrunk back to a span of 9 to 12 months.

His anterograde amnesia was profound. For at least 6 months after the onset of his illness, he had virtually no recall of episodic personal information. By lunch he could not recount reliably what he had done that morning. When asked how he felt, he would say that he had improved dramatically from the day before, that everything yesterday was a 'fog', and that he had now reached a 'new level of consciousness and clarity'. Formal assessment of recent memory confirmed this clinical impression: he was severely impaired across all verbal memory tasks, both with auditory and visual presentations. Story recall of the Logical Memory stories from the Wechsler Memory Scale—I (Wechsler, 1945) was 6 immediately (average normal = 10), but zero after a 30 min delay (average normal = 8): no information was recalled and there was no overt recognition that stories had previously been presented. Paired associate learning from the Wechsler Memory Scale was impaired and none of the hard associates were learned. He was similarly impaired on word list learning tasks (California Verbal Learning Test (Delis *et al.*, 1983)), recalling no more than 5 of 16 words. After a 30 min delay, both cued and free recall of the California word list were zero.

In contrast, he performed much better on nonverbal recent memory tasks, such as the Milner facial memory task (Milner, 1968), and the Benton visual recognition task (Benton, 1974). Immediate and delayed recall of the Rey Osterreith figure (Lezak, 1976), however, was abnormal.

*Follow-up testing*

Tests performed 7 months after his haemorrhage showed improvement in his memory quotient and paired associate learning. Twenty to 22 months after his haemorrhage, his full scale IQ had increased to 125, but his memory quotient remained more than 20 points below his verbal IQ, indicating isolated memory impairment. He recalled none of the logical memory stories on the Wechsler memory test after a 30 min delay, and on the California Verbal Learning Test he recalled only 3 of 16 words after distraction without delay, and zero of 16 with a 30 min delay, and his performance on the Peterson-Peterson auditory consonant trigram memory task was at least as impaired at 22 months as it had been 3 to 4 months after the haemorrhage.

## DISCUSSION

T.R.'s amnesia is similar to the classic amnesic syndromes described with bitemporal or diencephalic lesions (Butters and Miliotis, 1985). He had severe anterograde amnesia: he initially was disorientated, and remembered very little about daily events. His anterograde amnesia began to improve about 5 months after the haemorrhage, so that by 7 months he was usually orientated as to place and day, but even after 2 years he was unable to carry on the responsibilities of his previous job, and performed poorly on standardized tests of recent memory. He also demonstrated a circumscribed retrograde amnesia. Although he did well on some tests of remote memory (the Albert Remote Memory test and the Florida recent/remote memory battery), he had difficulty recalling with appropriate clarity and specificity personal memories for events occurring in the past 4 years, as demonstrated on a personal autobiographical test of memory. Finally, he had remarkably intact general intellectual functions: there were no consistent deficits on tests of 'frontal lobe' function, and language, praxis, and visuospatial functions that did not rely on memory were intact.

T.R.'s memory deficit was to some extent material-specific. Verbal tasks showed a consistent deficit; while tests of nonverbal memory, except for the Rey-Osterreith Complex Figure Test, were performed normally. Poor performance on the Rey Osterreith Complex Figure task, however, is seen in both right and left hemisphere-damaged patients. While T.R. had an abnormal rate of forgetting for verbal material, the rate of forgetting for nonverbal material was not significantly different from controls (*see* Appendix). The results are compatible with the proposal that the predominantly left-sided lesion in this case affected verbal more than nonverbal memory.

More detailed consideration of the results of neuropsychological testing of this patient are to be reported separately.

*Localization*

Although T.R. has a classic amnesic syndrome, extensive neuroradiological studies demonstrated that the lesions associated with his intracerebral haemorrhage spared the areas classically associated with amnesia: there were no lesions seen in the diencephalon (Victor *et al.*, 1971; Squire and Moore, 1979; Speedie and Heilman, 1982, 1983; Graff-Radford *et al.*, 1984; von Cramon *et al.*, 1985; Rousseaux *et al.*, 1986) or basal forebrain (Whitehouse *et al.*, 1981; Alexander and Freedman, 1983; Volpe and Hirst, 1983; Damasio *et al.*, 1985; Hepler *et al.*, 1985), and both medial temporal lobes (Scoville, 1954; Scoville and Milner, 1957; Cummings *et al.*, 1984; Zola-Morgan *et al.*, 1986) were free of evidence of a destructive lesion. The small lucency in the anterior hippocampus on the left (*see* fig. 3D) probably represents anomalous vessels: it remained lucent on T2 MRI studies (spin echo sequence: 2000 ms pulse repetition time; 90 ms echo delay), suggesting either calcium or blood, but it was not visible on the CT scan or



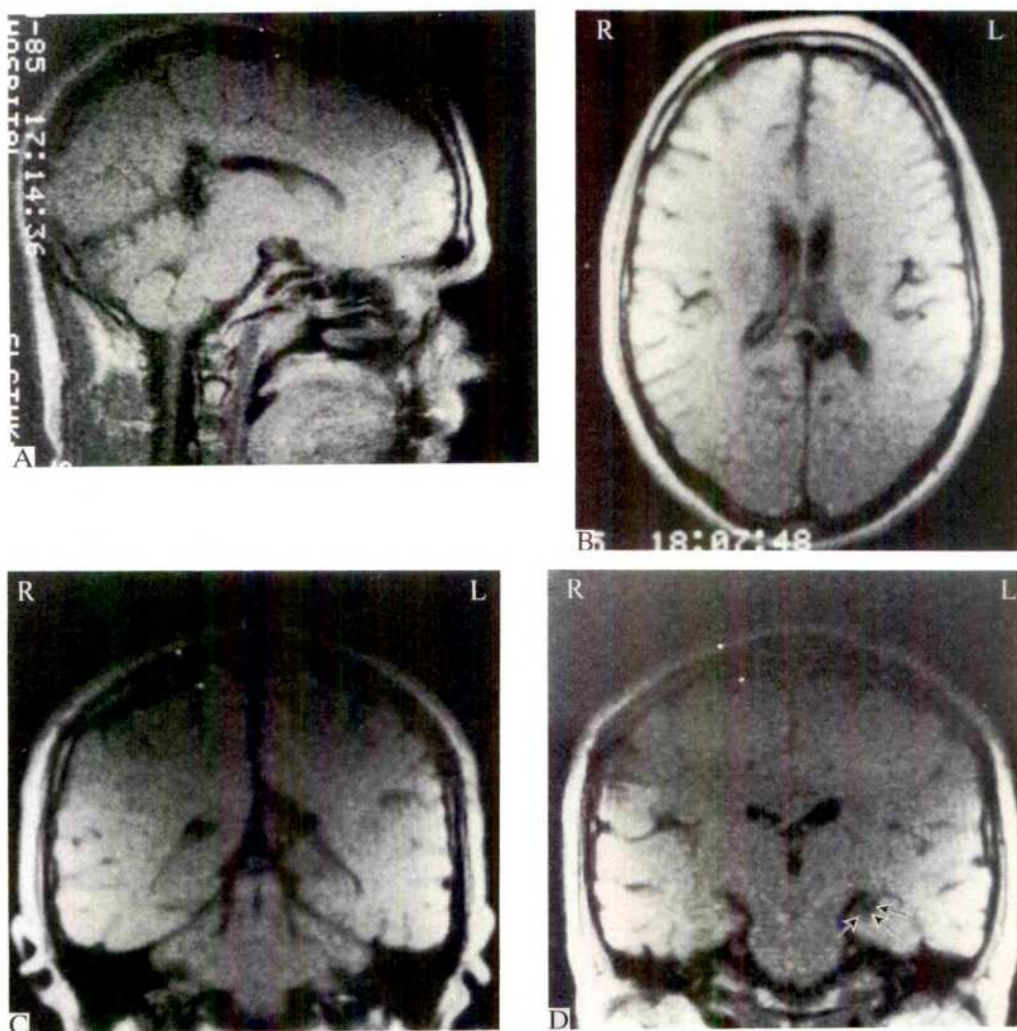


FIG. 3. MRI scan taken 9 months after the haemorrhage. These  $T_1$ -weighted images were taken using a spin echo pulse sequence with a 500 ms pulse repetition time and a 30 ms echo delay. Sagittal (A), axial (B), and coronal (C) views through the lesion. D, coronal view in the plane of the anterior portion of the hippocampus, demonstrating a small lucency on the left (arrowed). This was one of serial 6 mm coronal cuts, and the abnormality was not seen on any other section. This area also appeared lucent on  $T_2$ -weighted images.

angiogram. Coronal sections at 6 mm intervals encompassing the entire extent of the temporal lobes showed no other lesions. There were no lesions involving neocortex and subcortical damage was confined to the site of the principal lesion, plus a small lesion at the site of a temporary ventricular shunt in the right dorsolateral frontal lobe.

The CT study (fig. 1), the angiogram (fig. 2) and the MRI studies (fig. 3) all locate the pathology near the splenium of the corpus callosum. Two MRI scans, performed 3 and 9 months after the onset of his deficit (and 2 and 8 months after operation) demonstrated a defect in the splenium of the corpus callosum, and an



adjacent lesion posterolateral to the splenium, involving the cortex and subcortical white matter between the splenium and trigone of the left lateral ventricle. This is the location of the most posterior portion of the cingulate gyrus, which is composed principally of the retrosplenial cortex. In the white matter deep to this cortex runs the cingulate bundle. The neuroradiological studies lack the resolution to identify with certainty whether certain small structures, such as the fornix and stria terminalis, were damaged. In the ventricle, the fornix runs anterior and inferior to the site of maximal damage, but may have been damaged, and the hippocampal commissure, directly beneath the splenium may also have been involved. The stria terminalis, adjacent to the caudate nucleus in the inferolateral wall of the lateral ventricle, was lateral to the lesion, and was probably spared. There was no radiological or clinical evidence to suggest right hemisphere involvement.

#### *Pathogenesis of T.R.'s amnesia*

Damage to one or more of the above-mentioned structures is presumably responsible for T.R.'s amnesia. Memory loss sometimes occurs after section of the *corpus callosum* (Dimond *et al.*, 1977; Bentin *et al.*, 1984). This has been attributed to associated damage to the fornix and/or the hippocampal commissure, or to disconnection of the left hemisphere from the right medial temporal region in patients with dysfunctional left medial temporal structures (associated with seizures) (Ross, 1980). The first mechanism might apply to our patient, and will be discussed below. The second appears unlikely; there is little to suggest that our patient's left hippocampus was dysfunctional, and even if it were, a small lesion in the splenium would not be sufficient to disconnect the left hemisphere from the right hippocampus. Patients with cerebral infarctions in the distribution of the left posterior cerebral artery may also present acutely with amnesia (Geschwind and Fusillo, 1966; Damasio and Damasio, 1983). These patients sometimes have lesions in the splenium; however, when amnesic, they always have associated damage to medial temporal structures (Damasio and Damasio, 1983). Although their lesions often extend anteriorly to involve at least a portion of the hippocampus, they may also involve the retrosplenial cortex and cingulum, and the mechanism of memory loss may thus be similar to that in our patient.

Lesions of the bodies of the *fornix* (fig. 4, lesion 1) disconnect the hippocampus from the septum, anterior thalamus and mamillary bodies. Fornix lesions in monkeys produce mild memory impairment (Gaffan, 1974; Owen and Butler, 1981; Moss *et al.*, 1981; Carr, 1982; Bachevalier *et al.*, 1985*a, b*). Fornix lesions in humans have had variable effects on memory. There are reports of definite memory impairment after surgical section (Sweet *et al.*, 1959; Hassler and Riechert, 1957) or trauma (Grafman *et al.*, 1985), and there are also reports of normal memory after surgical section (Dott, 1938; Cairns and Mosberg, 1951; Garcia Bengochea *et al.*, 1954) or destruction by tumour (Woolsey and Nelson, 1975). The reports of normal memory have not included careful neuropsychological testing. Heilman and Sybert (1977) also pointed out that surgical section of the columns of the fornix

adjacent lesion posterolateral to the splenium, involving the cortex and subcortical white matter between the splenium and trigone of the left lateral ventricle. This is the location of the most posterior portion of the cingulate gyrus, which is composed principally of the retrosplenial cortex. In the white matter deep to this cortex runs the cingulate bundle. The neuroradiological studies lack the resolution to identify with certainty whether certain small structures, such as the fornix and stria terminalis, were damaged. In the ventricle, the fornix runs anterior and inferior to the site of maximal damage, but may have been damaged, and the hippocampal commissure, directly beneath the splenium may also have been involved. The stria terminalis, adjacent to the caudate nucleus in the inferolateral wall of the lateral ventricle, was lateral to the lesion, and was probably spared. There was no radiological or clinical evidence to suggest right hemisphere involvement.

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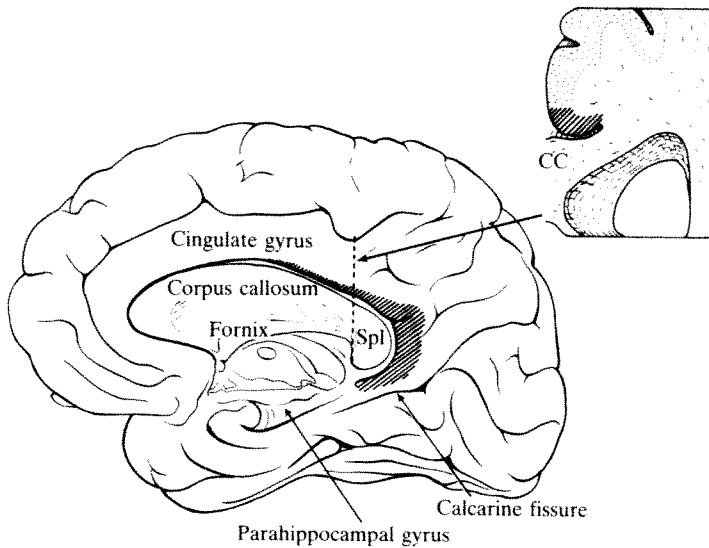


FIG. 5. The extent of the retrosplenial cortex on the medial aspect of the cerebral hemisphere is indicated by cross-hatching. *Inset* shows a partial coronal section at the level indicated by the dotted line. CC = corpus callosum. Spl = splenium.

primates, but it is clear from observations in various species that retrosplenial cortex is richly connected both to the anterior thalamic nuclei and to medial temporal structures. In the rabbit, the principal projections of the anteromedial and anterodorsal thalamic nuclei are to the granular retrosplenial cortex, while the anteroventral nucleus projects principally to the agranular retrosplenial cortex (Robertson and Kaitz, 1981; Jones, 1985). The lateral dorsal thalamic nucleus (considered to be one of the anterior thalamic nuclei) projects strongly to the cingulate cortex, agranular retrosplenial cortex, and presubiculum and parasubiculum (Jones, 1985). It has been demonstrated in monkeys and rodents that the retrosplenial cortex has reciprocal connections with subiculum and pre-subiculum and projects back to the anterior and lateral dorsal thalamus (Domesick, 1972; Rosene and Van Hoesen, 1977; Sorensen, 1980, Schwerdtfeger and Sarvey, 1983; Vogt and Miller, 1983). The fibres connecting the retrosplenial cortex with the thalamus and medial temporal lobe structures are carried in the *cingulate bundle* (Mufson and Pandya, 1984).

A lesion of the retrosplenial cortex and underlying cingulate bundle would therefore interrupt an alternative pathway from hippocampus to anterior thalamus (via the retrosplenial cortex). Perhaps more importantly, such a lesion would also interrupt input from the anterior and lateral dorsal thalamic nuclei to retrosplenial cortex and medial temporal lobe (fig. 4). This lesion might substantially disrupt communication between the anterior thalamus and hippocampus, and thus may have an effect similar to lesions in either of the structures that it disconnects.

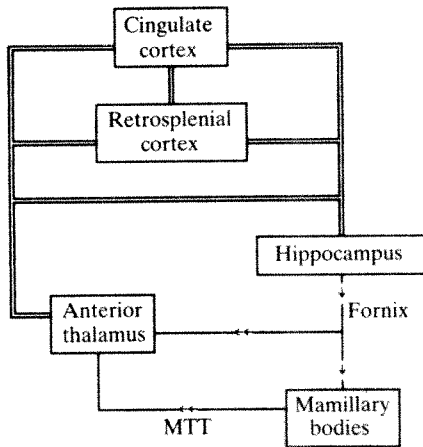


FIG. 6. Diagrammatic representation of Papez' circuit. The double lines indicate components of the cingulate bundle. MTT = mamillothalamic tract.

### *Papez' circuit revisited*

The cingulate bundle is a component of Papez' circuit (hippocampus—fornix—mamillary bodies—mamillothalamic tract—anterior thalamus—cingulate gyrus—cingulate bundle—hippocampus). Since the retrosplenial cortex also connects the anterior thalamus with medial temporal lobe structures, it may share functions with structures of Papez' circuit (figs 4, 6).

There is strong evidence that some of the structures in Papez' circuit mediate memory. Hippocampal lesions in humans (Scoville, 1954; Scoville and Milner, 1957; Penfield and Milner 1958; Milner and Teuber, 1968; Zola-Morgan *et al.*, 1986) and in nonhuman primates (Mishkin *et al.*, 1982; Zola-Morgan and Squire, 1986) produce severe and long-lasting amnesia. The evidence concerning fornix lesions has been summarized above. In humans, infarctions of the thalamus in the distribution of the tuberothalamic (polar thalamic) artery are often associated with amnesia. The territory of this artery includes the mamillothalamic tract and lateral dorsal nucleus (von Cramon *et al.*, 1985), and possibly the anterior nucleus proper (Graff-Radford *et al.*, 1984, 1985). In monkeys, medial thalamic lesions that involve either the anterior or dorsomedial nucleus cause mild amnesia, whereas lesions that involve both regions cause severe amnesia (Aggleton and Mishkin, 1983).

Evidence that mamillary body lesions cause amnesia is less convincing. Although all patients with Wernicke-Korsakoff syndrome have medial mamillary body lesions, Victor *et al.* (1971) found that dorsomedial thalamic lesions in this syndrome correlated better with amnesia. Mair *et al.* (1979), however, described 2 patients with Wernicke-Korsakoff disease whose medial thalamic lesions were very small and spared the dorsomedial nucleus; they considered the accompanying mamillary body lesions to be important. Monkeys with mamillary body lesions have demonstrated only mild impairments on delayed nonmatching to sample tests (Aggleton and Mishkin, 1985). As noted above, many fibres from the hippocampus

leave the fornix to go directly to the anterior thalamic nuclei, bypassing the mamillary bodies: this direct hippocampal-thalamic pathway might well compensate for damage to the mamillary bodies.

The limb of Papez' circuit from the anterior thalamus to the medial temporal lobe has not previously been implicated in memory. Cingulectomies performed for treatment of pain or emotional disorders do not result in long-standing memory disturbance (Teuber *et al.*, 1976), and lesions of the anterior portion of the cingulate gyrus produce only transient memory disturbance (Damasio and Van Hoesen, 1983). These lesions, however, are anterior to the portion of the cingulate bundle that contains projections from the anterior thalamus to retrosplenial cortex and medial temporal lobe. The present case raises the possibility that lesions placed more posteriorly in the cingulate and retrosplenial cortex, or in the cingulate bundle, or both, produce amnesia by disrupting Papez' circuit.

This case demonstrates again that communication between medial temporal and diencephalic structures is critical for normal memory function. This view has been strongly supported by the work of Mishkin and his colleagues in monkeys. They have shown that severe deficits can be seen in monkeys with lesions of the medial temporal lobes (Mishkin *et al.*, 1982), or the medial thalamus (including anterior and dorsomedial nuclei) (Aggleton and Mishkin, 1983), or the pathways connecting these regions (fornix and amygdalofugal pathways) (Bachevalier *et al.*, 1985a).

Mishkin has argued that the hippocampus-fornix-anterior thalamus pathway (part of Papez' circuit) and the amygdala-amygdalofugal-dorsomedial thalamus pathway can each in part compensate for lesions to the other: severe amnesia is seen only when both pathways are involved. Although this view is supported by the work of Mishkin and his colleagues in monkeys, and by the relative severity of the amnesia of H.M., Scoville's patient whose amygdalae and hippocampi were removed bilaterally for treatment of epilepsy, the compensation is only partial, since monkeys (Zola-Morgan and Squire, 1986) and humans (Cummings *et al.*, 1984; Zola-Morgan *et al.*, 1986) with bilateral lesions restricted to the hippocampus have significant and lasting memory deficits. T.R.'s lesion did not involve the amygdalo-dorsomedial thalamic pathway, and yet his memory loss, although not as severe as H.M.'s, was striking. T.R.'s intact right Papez' circuit was also insufficient to compensate for his unilateral lesion: in humans, hemisphere specialization has made verbal memory vulnerable to unilateral lesions (Speedie and Heilman, 1982; Graff-Radford *et al.*, 1984, 1985).

Although suggestive, a single case report with only radiological localization cannot establish the importance of a region in memory. The hypotheses that amnesia results from lesions in either retrosplenial cortex or the cingulate bundle (or both) can be tested by observing the effects of selective lesions in monkeys and other animals that can be trained on appropriate memory tasks. Such studies, currently in progress in our laboratory, may also help to clarify the relative contribution of different structures in this area to memory function.

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This case demonstrates again that communication between medial temporal and diencephalic structures is critical for normal memory function. This view has been strongly supported by the work of Mishkin and his colleagues in monkeys. They have shown that severe deficits can be seen in monkeys with lesions of the medial temporal lobes (Mishkin *et al.*, 1982), or the medial thalamus (including anterior and dorsomedial nuclei) (Aggleton and Mishkin, 1983), or the pathways connecting these regions (fornix and amygdalofugal pathways) (Bachevalier *et al.*, 1985a).

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Although suggestive, a single case report with only radiological localization cannot establish the importance of a region in memory. The hypotheses that amnesia results from lesions in either retrosplenial cortex or the cingulate bundle (or both) can be tested by observing the effects of selective lesions in monkeys and other animals that can be trained on appropriate memory tasks. Such studies, currently in progress in our laboratory, may also help to clarify the relative contribution of different structures in this area to memory function.



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## THE PRESENCE OF CALCITONIN GENE-RELATED PEPTIDE IN HUMAN CEREBROSPINAL FLUID

by S.J. WIMALAWANSA and I. MACINTYRE

(From the Endocrine Unit, Department of Chemical Pathology, Royal Postgraduate Medical School, London)

### SUMMARY

This study demonstrates the presence of calcitonin gene-related peptide (CGRP) in human cerebrospinal fluid (CSF) using specific and sensitive radioimmunoassay, together with gel-permeation and high performance liquid chromatography (HPLC). The median immunoreactive CGRP (i-CGRP) level from 158 CSF specimens was 8.0 pmol/l, as measured with an antiserum recognizing the whole molecule of CGRP (CC-2/1) and 12.0 pmol/l with an antiserum recognizing the C-terminal region of CGRP (CG-39).

CSF samples with high protein concentration ( $\geq 0.6$  g/l) had a median level of i-CGRP of 18.4 pmol/l when measured with antiserum CC-2/1 and 23.0 pmol/l with CG-39, while samples with 'normal' protein concentrations ( $< 0.6$  g/l) had much lower values, with median levels of 7.0 and 11.0 pmol/l, with the two antisera, respectively. Gel-permeation chromatography and HPLC studies revealed multiple peaks of i-CGRP, consistent with forms with different molecular weights. However, on HPLC, the major peak of i-CGRP corresponded to the elution position of the synthetic hCGRP<sub>(1-37)</sub> and was able to bind to a CGRP specific receptor preparation suggesting that it may be biologically active.

### INTRODUCTION

The existence of calcitonin gene-related peptide (CGRP) was predicted in the rat from a cDNA nucleotide sequence (Amara *et al.*, 1982; Rosenfeld *et al.*, 1983). Evidence of its existence in man was demonstrated by Morris *et al.* (1984), who isolated the human  $\alpha$ -CGRP from a medullary thyroid carcinoma. CGRP is widely distributed in a variety of tissues, including the central nervous system (CNS) (Rosenfeld *et al.*, 1983; MacIntyre, 1984; Skofitsch and Jacobowitz, 1985; Wimalawansa *et al.*, 1987), and is especially concentrated in the spinal cord (Gibson *et al.*, 1984; Wimalawansa *et al.*, 1987). Receptors for CGRP have been demonstrated in the nervous system of the rat (Goltzman and Mitchell, 1985; Wimalawansa *et al.*, 1987) and in man (Tschopp *et al.*, 1985). Intracerebroventricular (icv) injection of CGRP causes inhibition of gastric acid output (Lenz *et al.*, 1985), suppression

of food intake (Krahn *et al.*, 1984), reduction of the frequency and amplitude of the spontaneous growth hormone secretory pulse (Tannenbaum and Goltzman, 1985) and control of intestinal motility (Fargeas *et al.*, 1985). It has also been shown that CGRP is capable of altering the excitability of neurons in the rat forebrain (Twery and Moss, 1985).

CGRP circulates in the plasma of normal humans (Girgis *et al.*, 1985) and in the rat (Zaidi *et al.*, 1986). It is not known whether CGRP is able to cross the blood-brain barrier. In the present study the presence of i-CGRP in human CSF was demonstrated using a specific and sensitive radioimmunoassay (RIA) together with gel-permeation and high performance liquid chromatography (HPLC).

## MATERIALS AND METHODS

### *Samples*

From 158 patients undergoing diagnostic lumbar punctures, aliquots (0.5 ml  $\times$  2) of CSF samples were taken and stored at  $-20^{\circ}\text{C}$  with 200 KIU/ml Aprotinin (Trasylol) for RIA and the remaining CSF was pooled for chromatography. At the same time blood was collected in heparinized tubes from 24 patients and 200 KIU/ml Aprotinin was added. The plasma was separated and stored at  $-20^{\circ}\text{C}$  as described above. CSF protein concentrations were determined in individual CSF samples (Meulemans, 1960).

### *Stability of CGRP in CSF*

When CSF was stored with Aprotinin as described above, CGRP was found to be stable for  $>12$  months. When  $^{125}\text{I}$ -hCGRP was incubated with fresh CSF, it was found to be stable  $>2$  h at room temperature, as assessed by trichloro-acetic acid precipitation and HPLC.

### *Extraction of i-CGRP*

For gel-permeation chromatography, 100 ml of pooled CSF was treated with an acid mixture (Bennett *et al.*, 1977) and the peptides were extracted and partially purified using C-18 Sep-Pak cartridges (Waters Associates, Milford, MA, USA) as previously described (Girgis *et al.*, 1985). Materials not retained by the Sep-Pak cartridges were dialysed to remove acids and salts and then lyophilized. A further 150 ml of pooled CSF was extracted in the same way for HPLC.

### *Radioimmunoassay (RIA)*

Prior to RIA, HPLC and gel-permeation fractions were dissolved in 20  $\mu\text{l}$  of 0.01 M formic acid and neutralized with 750  $\mu\text{l}$  of 20 mM sodium phosphate buffer pH 7.4. RIA was performed using a nonequilibrium assay employing two antisera, a C-terminus specific antiserum (CG-39), and an antiserum recognizing the intact molecule of CGRP<sub>(1-37)</sub> (CC-2/1), as previously described (Wimalawansa *et al.*, 1987; Girgis *et al.*, 1985). Neat CSF and the reconstituted chromatographic fractions were assayed for i-CGRP, at least in two dilutions in duplicate and results were expressed as pmol/l in neat CSF, or fmol/fraction. In addition to RIA, HPLC fractions were further characterized by a highly specific radioreceptor assay (RRA) for CGRP (Wimalawansa and MacIntyre, 1987). Both  $\alpha$  and  $\beta$ -hCGRP fully cross reacted in all three assays.

### *Statistical analysis*

Differences of i-CGRP concentration between the 'groups with high and low proteins in the CSF' were analysed using the Mann-Whitney U test, since the data were not normally distributed; i-CGRP in plasma and CSF was analysed by the paired t test following log transformation and the correlations between CSF protein and i-CGRP were analysed by Spearman's rank correlation coefficient.

## RESULTS

*Immunoreactive CGRP in human CSF*

The dilution curves of i-CGRP in CSF samples were parallel to those of the synthetic hCGRP<sub>(1-37)</sub>. i-CGRP was measurable in 107 out of 158 CSF samples (68%) with antiserum CC-2/1 (median 8.0 pmol/l, range 2.5–86 pmol/l) and in 139 samples (88%) with antiserum CG-39 (median 11.0 pmol/l, range 2.5–98 pmol/l). In the CSF samples ( $n=113$ ) with protein concentrations  $<0.6$  g/l (mean  $\pm$  SEM,  $282 \pm 12$ ) the median value of i-CGRP was 7.0 pmol/l with the CC 2/1 and 11.0 pmol/l with the CG-39 antiserum (fig. 1). i-CGRP in the group with protein

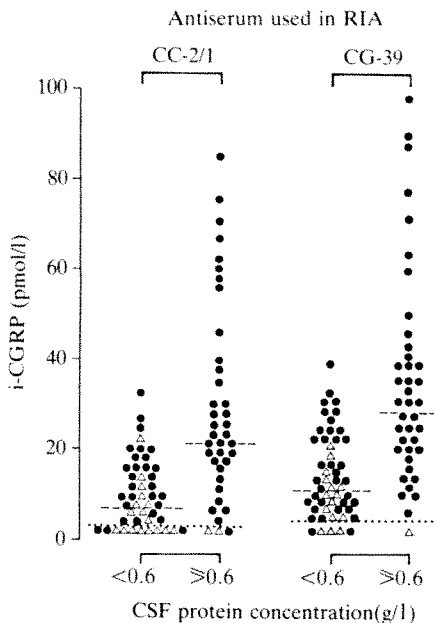


FIG. 1. Levels of i-CGRP in patients with 'normal' ( $<0.6$  g/l) ( $n=113$ ) and 'high' ( $\geq 0.6$  g/l) ( $n=45$ ) CSF proteins measured using CC-2/1 and CG-39 antisera. ● = denotes a single sample and △ 5 samples. --- = the median values; ... = the detection limit of the assay.

concentrations  $\geq 0.6$  g/l ( $849 \pm 36$ ) ( $n=45$ ), median values were 18.4 pmol/l and 23.0 pmol/l, respectively. The differences between the two groups were found to be highly significant ( $P < 0.001$ ) (fig. 1). No correlation was found between CSF i-CGRP levels and the age or the sex of the patients.

A positive correlation was found between i-CGRP and CSF total proteins. In the whole group correlation of CSF protein with the i-CGRP was  $r=0.54$  ( $P < 0.001$ ) with CC-2/1 antiserum and  $r=0.62$  ( $P < 0.001$ ) with CG-39. i-CGRP values obtained with the two antisera were highly correlated ( $r=0.95$ ,  $P < 0.001$ ). The level of i-CGRP when measured by antiserum CG-39 had a better correlation with the CSF total proteins, in both the  $<0.6$  g/l group ( $r=0.51$ ,  $P < 0.001$ ) and in the  $\geq 0.6$  g/l group ( $r=0.54$ ,  $P < 0.001$ ) in comparison with the CC-2/1 antiserum ( $r=0.41$  and  $r=0.47$ , respectively,  $P < 0.001$ ).

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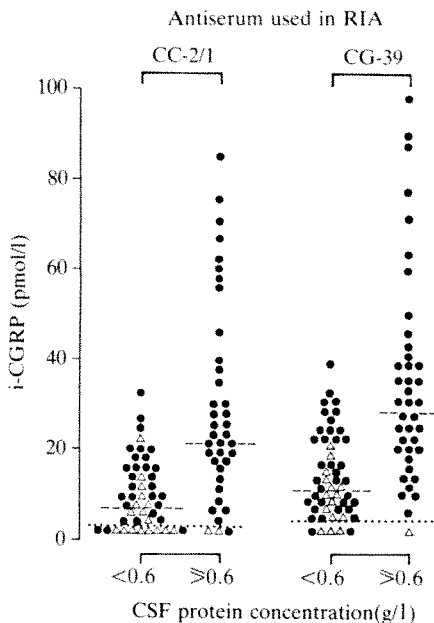


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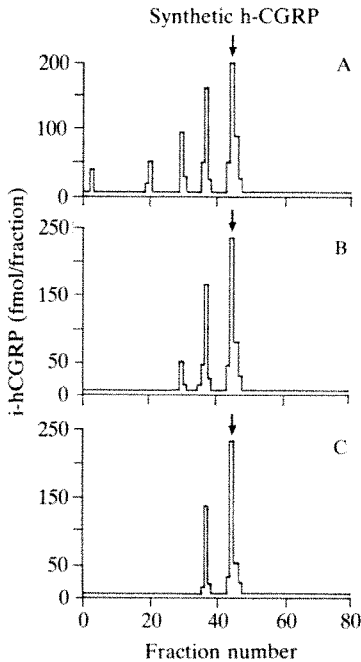


FIG. 3. High performance liquid chromatography of 150 ml of pooled human CSF. The CSF extracts were reconstituted in acetonitrile:water:TFA (28:71.8:0.2) and chromatographed on a Spherisorb 5 $\mu$  ODS column (25  $\times$  0.46 cm) using a linear gradient (28–44% acetonitrile, v/v, in aqueous TFA, 0.2%). Fractions (1 ml) were collected over 80 min, lyophilized and stored at  $-20^{\circ}\text{C}$  until assayed. Fractions were assayed with antisera CG-39 (A) and CC-2/1 (B) respectively, with RIA. Fractions were also measured for receptor active-CGRP by a specific radioreceptor assay (C).

#### *Correlation of plasma and CSF CGRP*

Higher levels of i-CGRP were detected in plasma than in the corresponding CSF ( $n = 24$ ) with both antisera ( $P < 0.001$ ). The mean level of protein concentration in these 24 CSF samples was  $491 \pm 78$  mg/l. The mean level of i-CGRP measured in the plasma was  $23.1 \pm 1.76$  pmol/l with antiserum CC-2/1 and  $29.3 \pm 2.9$  pmol/l with antiserum CG-39. In the CSF, i-CGRP levels were  $15.4 \pm 2.2$  pmol/l and  $19.2 \pm 2.5$  pmol/l, respectively. However, the correlations of i-CGRP in plasma were poor with their corresponding CSF levels ( $r = 0.33$  with antiserum CC-2/1 and  $r = 0.41$  with antiserum CG-39), and were statistically not significant.

#### DISCUSSION

In the present study we show that i-CGRP is present in the CSF. The presence of multiple immunoreactive forms of CGRP were identified, including the monomeric form. The dilution curves of i-CGRP in the CSF were parallel to those of synthetic hCGRP (1–37). i-CGRP profiles obtained with two antisera on gel-permeation studies indicate the existence of more than one immunological form of CGRP (fig. 2). In the gel-permeation chromatography of the Sep-Pak purified material, both antisera detected a major peak of i-CGRP, which coeluted with the synthetic hCGRP<sub>(1–37)</sub>. The other peaks of higher molecular weight forms may represent protein bound CGRP, large molecular weight forms including a precursor, or a

dimeric form. On the other hand, the later eluting i-CGRP peaks (fig. 2,y) which is recognized only by antiserum CG-39, is likely to be due to a C-terminal fragments of CGRP. However, further studies are necessary to characterize these different molecular weight forms of i-CGRP. It is possible that the antisera are cross reacting with some as yet unknown peptide present in the CSF. A similar pattern of multiple immunological forms of CGRP was found in human and in rat plasma (S.J. Wimalawansa, unpublished). HPLC studies of CSF extracts reaffirmed the immunological heterogeneity of CGRP in CSF (fig. 3). The major i-CGRP peak coeluted with the intact synthetic hCGRP. It is possible that the minor peak represents the oxidized form of  $\beta$ -hCGRP (methionine-sulphoxide). Nevertheless, the data from these two chromatographic systems suggest that the major component of i-CGRP in the CSF (whether  $\alpha$ ,  $\beta$ , or both) represents the monomeric form of CGRP.

The transport of circulating substances into the brain, in general, is known to be limited selectively and strictly by the blood-brain barrier (Pardridge, 1981). The presence of several peptide hormones has been reported in the CSF of man (Greco *et al.*, 1970; Becker *et al.*, 1980; Morimoto *et al.*, 1982) and in other mammals (Knigge and Joseph, 1974), and is thought to reflect an important pathway in neuroendocrine integration (Rodríguez, 1976). It has been postulated that several of these peptides may exert a direct influence upon CNS function (Becker *et al.*, 1980). Apart from acting as a buffer to external pressure waves, CSF is thought to act as a means for removing metabolites from cerebral tissues (Johnson, 1972).

CGRP has been shown to potentiate the irritant effects of intrathecally administered substance P in rat (Wiesenfeld-Hallin *et al.*, 1984). It has also been suggested that CGRP may noncompetitively inhibit substance P degradation by acting as an alternative substrate for an endopeptidase isolated from human CSF (Le Greves *et al.*, 1985). Nevertheless, it is not known whether i-CGRP in the CSF has any physiological role, or whether it originates from the peripheral blood, or emanates from the CNS. The significantly different levels of i-CGRP found in the CSF, in comparison to plasma, is likely to be due to the inability of CGRP to cross the blood-brain barrier and thus strengthen the possibility of the origin of CSF-CGRP within the nervous tissue. However, in CSF, i-CGRP levels correlate well with protein concentration ( $P < 0.001$ ). Some of the CSF samples, particularly the ones with high protein concentration, were from patients with infections of brain or meninges and the higher levels may reflect loss of integrity of the blood-brain barrier due to inflammation and subsequent passage of CGRP into the CSF.

Ninety per cent of the patients with CSF protein  $\leq 0.6$  g/l were found to have infections in the CNS or the meninges. In these samples, antiserum CG-39 gave consistently higher i-CGRP levels in comparison with values obtained with antiserum CC-2/1. In addition to the whole molecule of CGRP, antiserum CG-39 recognizes the C-terminal fragments of CGRP. This finding suggests the presence



of increasing amounts of immunoreactive CGRP fragments in these samples and explains partly the higher levels of i-CGRP detected with CG-39 antiserum, in comparison with CC-2/1. CSF from patients with both high and low protein concentrations were pooled for the chromatographic studies described in this study. It is therefore still a possibility that high concentrations of proteins in the CSF may affect the proportion of the protein-bound CGRP, thereby affecting the high molecular weight i-CGRP peaks to 'free CGRP', which is presumably more biologically active.

Finally, the ability of CGRP in CSF to bind to specific CGRP receptors (fig. 3c) in conjunction with the demonstration of multiple biological effects following icv injection (Krahn *et al.*, 1984; Fargeas *et al.*, 1985; Lenz *et al.*, 1985; Tannenbaum and Goltzman, 1985), suggests that CGRP may have physiological roles in the CNS.

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# AMINO ACID NEUROTRANSMITTER ABNORMALITIES IN HUNTINGTON'S DISEASE AND THE QUINOLINIC ACID ANIMAL MODEL OF HUNTINGTON'S DISEASE

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## SUMMARY

Concentrations of gamma-aminobutyric acid (GABA), glutamate, aspartate, and taurine were measured in postmortem tissue from the brains of patients with Huntington's disease (HD) and in the quinolinic acid (QA) lesioned rat striatum. The aim of the study was to assess further the ability of the QA model of HD to reproduce the neurochemical features of the disease.

Nine cortical and 9 subcortical regions were examined from 17 pathologically graded cases of HD and 10 controls. Significant reductions in both GABA and glutamate were found in HD striatum. The reductions were greater in the more severely affected grades of HD, and there was a gradient of amino acid loss across the striatal nuclei (caudate > putamen > nucleus accumbens) which was consistent with the known pattern of pathological involvement. Taurine and aspartate concentrations showed no significant change. GABA reductions were found in both segments of the globus pallidus (external > internal) and both parts of the substantia nigra (reticulata > compacta). In advanced cases of HD, there were significant reductions in glutamate in Brodmann cortical areas 3–1–2, 6, 9, and 17, but GABA, aspartate, and taurine were unaltered in the cortex.

The QA lesions reproduced the striatal deficits of both GABA and glutamate but, in contrast to HD, there was a decrease in taurine, possibly due to species differences. Chronic QA lesions resulted in a secondary dying back of corticostriatal glutamatergic terminals, but did not produce a change in cortical glutamate concentration. This suggests that reductions in cortical glutamate in HD may reflect a primary loss of glutamatergic neurons. Our findings extend previous observations on amino acid neurotransmitters in HD and, with the exception of taurine, confirm the general applicability of the QA model.

## INTRODUCTION

Huntington's disease (HD) is a progressive neurological disorder characterized by choreiform movements and dementia. Symptoms typically begin in the fourth and

fifth decades (Huntington, 1872; Martin, 1984). It is a genetic disorder displaying autosomal dominant inheritance. The defective gene has been localized to the short arm of chromosome 4 (Gusella *et al.*, 1983), but how the abnormal gene product determines the pathological and clinical features of the disease remains unclear. The most profound neuropathological changes occur in the striatum where there is marked atrophy, neuronal loss, and astrogliosis (Bruyn *et al.*, 1979; Vonsattel *et al.*). Similar but milder changes are also apparent in other nuclei of the basal ganglia, and there is often cortical atrophy. The striatum contains a variety of neuronal types, and both the analysis of neurochemical markers (Beal and Martin, 1986b) and immunohistological studies (Kowall *et al.*, 1987) have helped to clarify the status of these neurons in HD. Whereas the type II spiny projection neurons are particularly vulnerable to the disease process (Lange *et al.*, 1976), the medium and large aspiny neurons are selectively spared (Dawbarn *et al.*, 1985; Ferrante *et al.*, 1985, 1986). Thus the concentrations of gamma-aminobutyric acid (GABA) and the neuropeptides substance P, met-enkephalin, and dynorphin, which are all biochemical markers for spiny projection neurons, are decreased in HD (Perry *et al.*, 1973; Emson *et al.*, 1980; Dawbarn *et al.*, 1986), and the neuropeptides somatostatin and neuropeptide Y, which are colocalized in medium aspiny neurons, are increased in concentration (Aronin *et al.*, 1983; Nemeroff *et al.*, 1983; Dawbarn *et al.*, 1985).

A detailed knowledge of the neurochemical pathology of a neurodegenerative illness allows animal models of that illness to be tested. The excitotoxin model of HD was proposed after the demonstration that kainic acid, an excitotoxin extracted from kelp, could produce neuronal death and gliosis when injected into the striatum (Coyle and Schwarcz, 1976; McGeer and McGeer, 1976). However, kainic acid neither produces a lesion in which somatostatin neurons are spared (Beal *et al.*, 1985) nor appears to exist in mammalian tissues. These two criteria are fulfilled by the excitotoxin quinolinic acid (QA), an endogenous metabolite of tryptophan in the kynurenine pathway. We have shown that intrastriatal QA can replicate the neurochemical features of HD since it depletes GABA and substance P and leaves somatostatin and neuropeptide Y unaltered (Beal *et al.*, 1986a). It is therefore possible that an abnormality of QA metabolism underlies the pathogenesis of HD (Schwarcz *et al.*, 1984). The aim of this study was to investigate the status of neurons that use GABA, glutamate, aspartate, and taurine as neurotransmitters or neuromodulators in —HD and in the QA model of HD.

## METHODS

### *Postmortem human studies*

The brains of 17 patients with HD and 10 patients without neurological or psychiatric illness were removed at autopsy and divided sagittally in the midline. One hemisphere was fixed in 10% formaldehyde for a detailed neuropathological examination, and the other was stored at  $-70^{\circ}\text{C}$

until dissection. The frozen hemisphere was dissected on a steel plate at  $-10^{\circ}\text{C}$  and then stored at  $-70^{\circ}\text{C}$  until neurochemical analysis (Bird and Iversen, 1974). Cortical regions were dissected according to Brodmann areas. The substantia nigra was divided into its two parts on the basis of the melanin-staining neurons contained in the pars compacta.

The HD brains were divided into four neuropathological grades according to the system of Vonsattel *et al.* (1985). Grade 1 cases show no atrophy of the caudate macroscopically, but are characterized by moderate astrocytosis and a neuronal loss of up to 50% in the caudate nucleus. Grade 2 cases show neuronal loss, astrocytosis, and mild macroscopical atrophy of the caudate, but the convexity of the caudate is retained. Grade 3 cases show severe neuronal loss with astrocytosis, and the atrophy has progressed to a degree where the ventricular surface of the caudate is straight in a coronal section. Grade 4 is assigned to severe cases with marked atrophy. The caudate becomes concave and is often just a thin strip of gliotic tissue. Neurons are severely depleted. For the purposes of neurochemical evaluation, grades 1 and 2 were combined into a group labelled as mildly affected. Grades 3 and 4 were combined into a group labelled as severely affected. The clinical data for these groups and for the control group are outlined in Table 1.

TABLE 1. CLINICAL AND PATHOLOGICAL DATA

|                         | <i>Huntington's disease</i>                                                                                                          |                                                                                                                      | <i>Control</i>                                                                        |  |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--|
|                         | <i>Mild</i>                                                                                                                          | <i>Severe</i>                                                                                                        |                                                                                       |  |
| No. of cases (grade)    | 7 (I-3; II-4)                                                                                                                        | 10 (III-5; IV-5)                                                                                                     | 10                                                                                    |  |
| Sex distribution        | Male - 3<br>Female - 4                                                                                                               | Male - 4<br>Female - 6                                                                                               | Male - 6<br>Female - 4                                                                |  |
| Age at death (yrs)      | $62.1 \pm 7.5$                                                                                                                       | $50.1 \pm 12.2$                                                                                                      | $70.6 \pm 15.0$                                                                       |  |
| Postmortem interval (h) | $10.4 \pm 5.8$                                                                                                                       | $11.0 \pm 6.8$                                                                                                       | $11.2 \pm 5.9$                                                                        |  |
| Cause of death          | Pneumonia 4<br>Respiratory failure 1<br>Ischaemic heart disease 1<br>Unknown 1                                                       | Pneumonia 8<br>Unknown 2                                                                                             | Pneumonia 4<br>Ischaemic heart disease 4<br>Carcinoma 1<br>Ruptured aortic aneurysm 1 |  |
| Antemortem drugs        | Major tranquilizer 3<br>Tricyclic antidepressant 2<br>Benzodiazepine 1<br>Anticholinergic 1<br>Steroids 1<br>Diuretic 1<br>Unknown 1 | Major tranquilizer 1<br>Benzodiazepine 3<br>Antihistamine 1<br>Barbiturate 1<br>Hydantoin 1<br>Opiate 1<br>Unknown 2 | Diuretic 1<br>Beta-blocker 1                                                          |  |

Figures are numbers of cases or means  $\pm$  SD.

### *Animal studies*

The effect of a single dose of intrastriatal QA on striatal amino acid and neuropeptide concentrations was examined in the rat over two postinjection time intervals: 7 days (acute) and 60 days (chronic). The aim of comparing these two time intervals was the assessment of time-dependent secondary tissue changes on the neurochemical markers. Such secondary changes might include striatal atrophy and neurotransmitter down-regulation, both possible consequences of the QA-induced neuronal loss. The effect of a limited decortication was also examined alone and in conjunction with both acute and chronic QA lesions. The contribution of the glutamate and aspartate in corticostriatal nerve terminals to total striatal concentrations would be determined in this way. In addition, we could examine whether a secondary dying back of the corticostriatal tract was a feature of the chronic QA lesion by determining the extent to which decortication reduced striatal glutamate

or aspartate in both acute and chronic groups. Preliminary studies had shown that a 240 nmol injection of QA produced a satisfactory striatal lesion without extension into the cortex and that the corticostriatal tract could be lesioned maximally by a surgical ablation of the anterolateral frontal cortex as depicted in fig. 1.

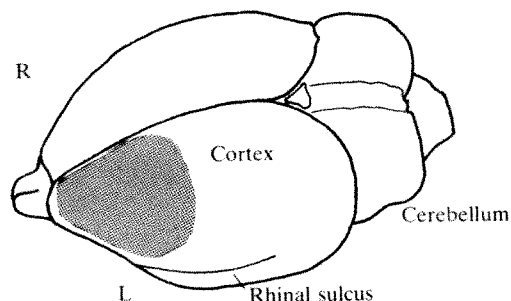


FIG. 1. Diagram of rat brain showing the extent of the decortication (stippled area).

Male Sprague-Dawley rats (150–200 g) were housed with free access to food and water. Animals were allotted to one of six groups: (1) control, in which animals received a unilateral intrastriatal injection of 240 nmol nicotinic acid; (2) decortication, in which the cortex was removed by suction (fig. 1) 5 days before being killed; (3) acute, in which animals received a unilateral intrastriatal injection of 240 nmol QA 7 days before killing; (4) acute plus decortication, in which the animals received a unilateral intrastriatal injection of QA 7 days before killing and a decortication 5 days before killing; (5) chronic, in which animals received a unilateral intrastriatal injection of 240 nmol QA 60 days before killing; (6) chronic plus decortication, in which the animals received a unilateral intrastriatal injection of QA 60 days before killing and a decortication procedure 5 days before killing.

Intrastriatal injection of QA and nicotinic acid were undertaken as described previously (Beal *et al.*, 1986a). In the few hours postinjection with QA, the rats were observed to 'rotate' and to 'barrel-roll', both physiological effects of this compound's excitatory action. These phenomena were not observed following injection with nicotinic acid. For the decortication procedure, an area of the skull over the left hemisphere of the brain was removed to allow access to the dorsal and anterolateral aspects of the hemisphere. A small bore metal tube to which a mild vacuum had been applied was used to remove the cortex. The tube was specially shaped to allow the removal of the lateral cortex down to the level of the rhinal sulcus without disturbing the striatum. The cortex was removed down to the corpus callosum and the space packed with Gel-foam, which had a haemostatic action. The animals were given a prophylactic dose of penicillin (125,000 IU, i.m.). The survival rate of this procedure was greater than 80%. In the postoperative period, these animals showed signs of a contralateral hemiplegia, but they recovered in the days before being killed. Preliminary studies showed that the unilateral ablation of the corticostriatal tract from such a lesion produced a maximal depletion in striatal glutamate and aspartate concentrations of about 35%. In accordance with previous reports (Fonnum *et al.*, 1981), extending the cortical lesion posteriorly did not deplete these amino acids further.

Animals were killed by decapitation. The brains were then quickly removed and dissected on an ice-cold plate. A coronal slab of brain was dissected with a parallel pair of razor blades 2 mm apart. The striatum from both sides, together with the overlying cerebral cortex, was placed in 0.5 ml ice-cold 50% methanol:water (v/v) and stored at  $-35^{\circ}\text{C}$  until neurochemical analysis. For the midbrain dissections, the substantia nigra was identified by its dark staining and then removed together with the underlying tissue.

### *Amino acid assay*

Approximately 150 mg of tissue from the postmortem human samples was weighed and placed in 1 ml of ice-cold 50% methanol:water (v/v). These and the previously suspended rat samples were homogenized by sonication for 20 s. The homogenates were centrifuged at 15,000 g for 6 min. Samples of supernatant were analysed for amino acids by a method using o-phthaldialdehyde/2-mercaptoethanol derivatization followed by high performance liquid chromatography with electrochemical detection (Ellison *et al.*, 1987). Amino acid concentrations were quantitated by peak height which was linear over the range of the assay.

### *Neuropeptide and protein assays*

The neuropeptides somatostatin, neuropeptide Y, and substance P are poorly extracted in methanol. Therefore, the samples on which peptide estimations were performed were acidified by the addition of 40  $\mu$ l 6 N HCl (final concentration 0.1 N HCl). The samples were sonicated for a further 10 s to resuspend the pellets and to allow extraction of the peptides. The samples were then centrifuged and aliquots were taken for radioimmunoassay. Radioimmunoassays for somatostatin-like immunoreactivity (SLI), neuropeptide Y-like immunoreactivity (NPYLI), and substance P-like immunoreactivity (SPLI) were carried out as previously described (Arnold *et al.*, 1982; Beal *et al.*, 1986c, d). Protein determinations were performed on tissue pellets using the method of Bohlen *et al.* (1973).

### *Data analysis*

Statistical comparisons were made by the unpaired Student's *t* test. Results are expressed as the mean  $\pm$  SEM, and concentration changes as a percentage of the control values.

## RESULTS

### *Huntington's disease*

The amino acid alterations in HD striatum are displayed in fig. 2. GABA was significantly decreased in all three nuclei of the striatum in the severely affected (grades 3 and 4) group of HD cases. The largest deficit (control,  $2.26 \pm 0.17$   $\mu$ mol/g wet weight; HD,  $0.60 \pm 0.07$   $\mu$ mol/g wet weight) was found in the caudate, and the decrease was greater in the putamen (control,  $2.27 \pm 0.22$ ; HD,  $0.98 \pm 0.13$ ) than in the nucleus accumbens (control,  $3.11 \pm 0.40$ ; HD,  $1.69 \pm 0.20$ ). In the mildly affected (grades 1 and 2) group, the largest GABA deficit (control,  $2.26 \pm 0.17$ ; HD,  $1.04 \pm 0.16$ ) was also found in the caudate. The putamen showed a significant decrease of 41% (control,  $2.27 \pm 0.22$ ; HD  $1.35 \pm 0.18$ ), but GABA was unaltered in the nucleus accumbens. Thus there was a gradient of GABA loss across the striatal nuclei (caudate > putamen > accumbens), and within these nuclei the more severely affected neuropathological group showed the greater deficits. The same pattern was seen for striatal deficits in glutamate. In the severely affected HD group, this amino acid was significantly decreased by 39% in the caudate (control,  $9.61 \pm 0.47$ ; HD,  $5.87 \pm 0.52$ ), by 27% in the putamen (control,  $9.81 \pm 0.60$ ; HD,  $7.17 \pm 0.47$ ), and by 19% in the accumbens (control,  $8.04 \pm 0.48$ ; HD,  $6.51 \pm 0.31$ ). Glutamate was not altered significantly in the mildly affected HD group. Aspartate was not altered significantly in any of the striatal nuclei. Although HD striatal taurine values did not differ significantly from controls, the mean values across the

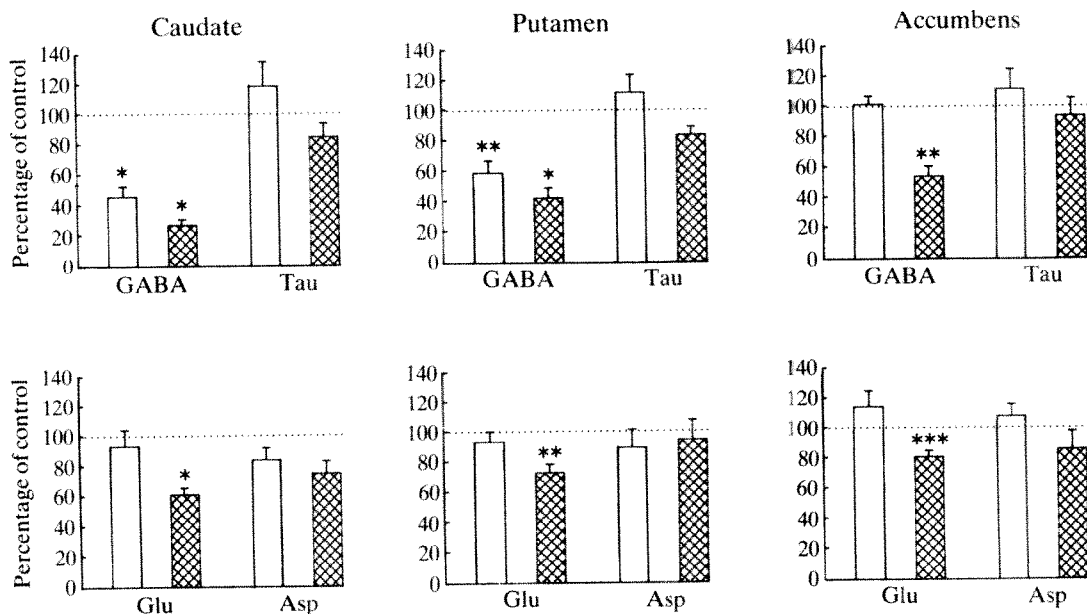


FIG. 2. Amino acid levels in HD striatum as a percentage of control levels (n=7). Open bars signify mild (grades 1 and 2) cases (n=7); hatched bars signify severe (grades 3 and 4) cases (n=7). Significance levels are as follows: \*P < 0.001, \*\*P < 0.01, \*\*\*P < 0.05. Error bars indicate SEM.

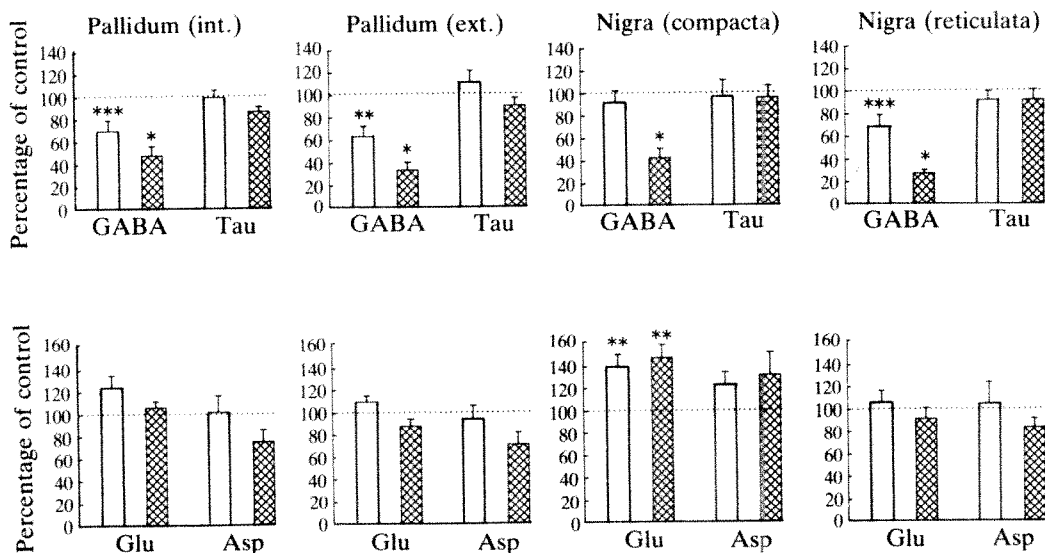


FIG. 3. Amino acid levels in two segments of HD globus pallidus and substantia nigra as a percentage of control levels (n=7). Int. = internal segment; Ext. = external segment; open bars signify mild (grades 1 and 2) cases (n=7); hatched bars signify severe (grades 3 and 4) cases (n=7). Significance levels are as follows: \*P < 0.001, \*\*P < 0.01, \*\*\*P < 0.05. Error bars indicate SEM.



three nuclei for the mildly affected group were all greater than control values, and the mean values for the severely affected group were all smaller. The difference between taurine values for the two HD groups was significant ( $P < 0.05$ ) in the caudate and putamen.

Significant decreases in GABA (fig. 3) were seen in both segments of the globus pallidus (external: control,  $3.67 \pm 0.24$ ; HD 1 and 2,  $2.36 \pm 0.33$ ; HD 3 and 4,  $1.23 \pm 0.24$ ; internal: control,  $4.22 \pm 0.28$ ; HD 1 and 2,  $2.95 \pm 0.43$ ; HD 3 and 4,  $2.07 \pm 0.33$ ). The external segment showed greater deficits, and again the more severely affected neuropathological group had lower values. Glutamate, aspartate, and taurine values in both segments did not differ significantly from control values. Both HD groups showed decreased GABA levels (fig. 4) in the pars reticulata of the substantia nigra (control,  $4.04 \pm 0.38$ ; HD 1 and 2,  $2.79 \pm 0.43$ ; HD 3 and 4,  $1.13 \pm 0.12$ ). Only in the severely affected HD group was GABA significantly decreased in the pars compacta of the substantia nigra (control,  $3.91 \pm 0.50$ ; HD 1 and 2,  $3.61 \pm 0.15$ ; HD 3 and 4,  $1.73 \pm 0.10$ ). Glutamate was increased in both

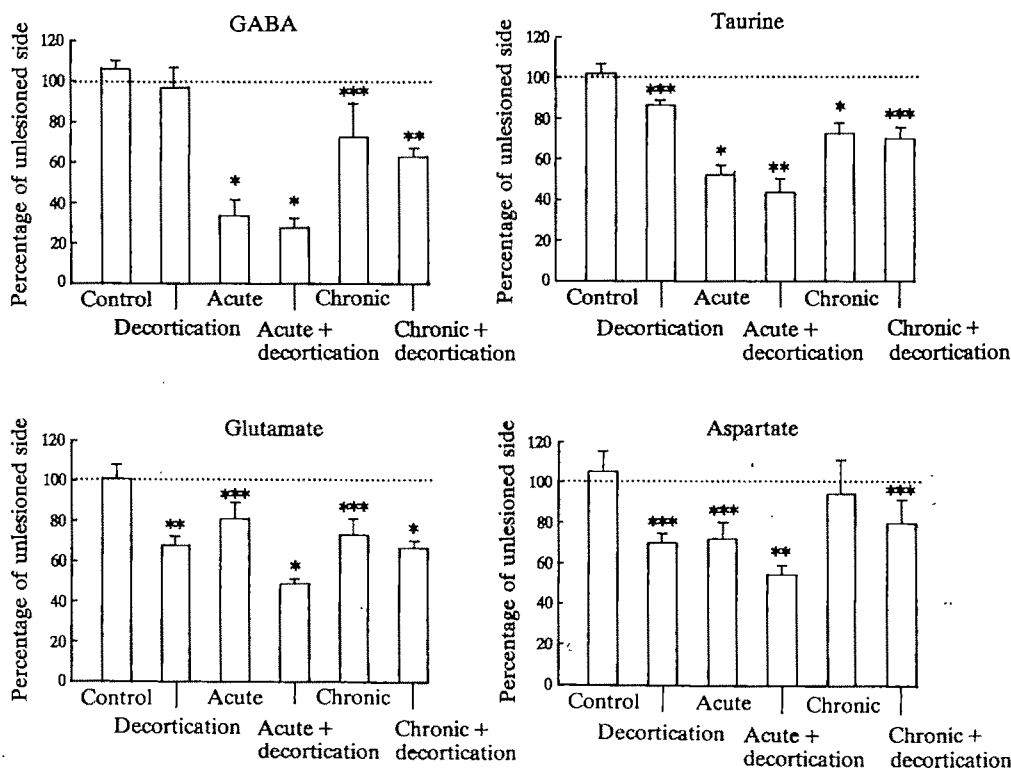


FIG. 4. Amino acid levels in rat corpus striatum from control and 5 lesioned groups (see text). Levels shown are from the lesioned side and are expressed as a percentage of the unlesioned side. Letters indicate significant differences when compared with unlesioned controls (100%). Significant differences between QA lesioned groups with decortication and QA lesioned groups without decortication were seen for glutamate ( $P < 0.01$ ) and aspartate ( $P < 0.05$ ) in the acute versus acute plus decortication group comparisons. Significance levels are as follows: \* $P < 0.001$ , \*\* $P < 0.01$ , \*\*\* $P < 0.05$ . Error bars indicate SEM.

groups in the pars compacta, but not in the pars reticulata of the substantia nigra (compacta: control,  $6.28 \pm 0.40$ ; HD 1 and 2,  $8.78 \pm 0.62$ ; HD 3 and 4,  $9.30 \pm 0.67$ ). Aspartate and taurine were unchanged in the substantia nigra. In other subcortical areas (Table 2), the only significant change among the amino acids was a 50%

TABLE 2. AMINO ACID LEVELS IN SUBCORTICAL AREAS (nmol/mg PROTEIN)

| Region                            | Group      |      | Glutamate        | GABA             | Aspartate      | Taurine        | Alanine        |
|-----------------------------------|------------|------|------------------|------------------|----------------|----------------|----------------|
| Hippocampus                       | Control    | (10) | $112.0 \pm 8.1$  | $10.4 \pm 1.1$   | $25.8 \pm 3.3$ | $12.7 \pm 1.2$ | $15.9 \pm 1.4$ |
|                                   | Huntington | (9)  | $110.0 \pm 6.4$  | $13.8 \pm 1.3$   | $20.5 \pm 2.7$ | $10.7 \pm 0.6$ | $14.9 \pm 1.6$ |
| Caudate                           | Control    | (6)  | $85.9 \pm 8.6$   | $9.8 \pm 0.9$    | $24.0 \pm 4.2$ | $6.9 \pm 0.7$  | $10.5 \pm 1.1$ |
|                                   | Huntington | (5)  | $107.0 \pm 14.7$ | $10.0 \pm 1.6$   | $24.9 \pm 2.6$ | $8.9 \pm 1.6$  | $12.8 \pm 1.4$ |
| Subthalamic nucleus               | Control    | (4)  | $56.8 \pm 2.2$   | $21.9 \pm 1.0$   | $24.7 \pm 3.5$ | $8.6 \pm 1.0$  | $13.2 \pm 2.1$ |
|                                   | Huntington | (8)  | $64.3 \pm 4.3$   | $18.0 \pm 3.1$   | $29.6 \pm 3.7$ | $6.5 \pm 0.5$  | $12.2 \pm 0.7$ |
| Ventrolateral nucleus of thalamus | Control    | (6)  | $96.6 \pm 7.2$   | $10.2 \pm 1.0$   | $36.3 \pm 3.8$ | $6.2 \pm 0.3$  | $15.6 \pm 0.9$ |
|                                   | Huntington | (6)  | $88.6 \pm 7.9$   | $10.3 \pm 1.7$   | $33.4 \pm 3.7$ | $6.0 \pm 0.7$  | $12.8 \pm 1.0$ |
| Anterior nucleus of thalamus      | Control    | (7)  | $88.7 \pm 6.8$   | $9.3 \pm 0.9$    | $20.9 \pm 0.9$ | $6.3 \pm 0.7$  | $13.6 \pm 1.6$ |
|                                   | Huntington | (6)  | $78.3 \pm 15.7$  | $14.0 \pm 1.8^*$ | $21.1 \pm 4.6$ | $6.9 \pm 1.2$  | $15.1 \pm 2.5$ |
| Dorsomedial nucleus of thalamus   | Control    | (7)  | $137.0 \pm 12.4$ | $11.8 \pm 1.3$   | $25.4 \pm 2.5$ | $7.1 \pm 0.7$  | $17.0 \pm 1.0$ |
|                                   | Huntington | (6)  | $111.0 \pm 14.1$ | $11.2 \pm 1.4$   | $22.3 \pm 3.3$ | $5.5 \pm 0.7$  | $15.2 \pm 1.0$ |

Values are means  $\pm$  SEM. The number of cases (grades 3 and 4) is in parentheses. \* $P < 0.05$ . GABA = gamma-aminobutyric acid.

increase in GABA in the anterior nucleus of the thalamus. Significant 16–20% decreases in glutamate concentration (Table 3) were found in Brodmann areas 3–1–2, 6, 9 and 17 of HD cortex, but other amino acids were unchanged. There was no correlation between amino acid levels and postmortem interval in any area.

TABLE 3. AMINO ACID LEVELS IN 9 CORTICAL AREAS (nmol/mg PROTEIN)

| Region            | Group      |      | Glutamate           | GABA           | Aspartate      | Taurine        | Alanine        |
|-------------------|------------|------|---------------------|----------------|----------------|----------------|----------------|
| Frontal           | Control    | (10) | $90.9 \pm 4.8$      | $9.1 \pm 0.7$  | $18.6 \pm 1.2$ | $6.9 \pm 0.5$  | $9.5 \pm 0.6$  |
| Area 9            | Huntington | (10) | $76.5 \pm 3.2^*$    | $10.2 \pm 0.8$ | $18.3 \pm 2.0$ | $5.7 \pm 0.4$  | $8.0 \pm 0.3$  |
| Frontal pole      | Control    | (5)  | $99.4 \pm 3.8$      | $13.0 \pm 1.8$ | $21.1 \pm 2.5$ | $7.8 \pm 1.0$  | $11.0 \pm 0.8$ |
| Area 10           | Huntington | (7)  | $94.8 \pm 5.6$      | $14.6 \pm 1.2$ | $20.7 \pm 1.2$ | $7.2 \pm 0.5$  | $9.8 \pm 0.6$  |
| Inferior frontal  | Control    | (5)  | $104.0 \pm 15.4$    | $10.5 \pm 1.1$ | $17.9 \pm 2.4$ | $6.4 \pm 0.8$  | $9.5 \pm 1.4$  |
| Area 11           | Huntington | (9)  | $100.0 \pm 8.1$     | $11.1 \pm 1.0$ | $20.4 \pm 2.2$ | $7.0 \pm 0.5$  | $8.7 \pm 0.8$  |
| Premotor          | Control    | (10) | $87.6 \pm 6.5$      | $8.9 \pm 0.9$  | $22.5 \pm 3.6$ | $7.6 \pm 0.6$  | $10.1 \pm 0.9$ |
| Area 6            | Huntington | (10) | $71.0 \pm 4.1^*$    | $10.8 \pm 0.8$ | $22.3 \pm 3.2$ | $6.4 \pm 0.7$  | $8.4 \pm 0.5$  |
| Postcentral       | Control    | (9)  | $96.3 \pm 5.8$      | $13.6 \pm 1.0$ | $18.9 \pm 1.0$ | $8.4 \pm 0.6$  | $15.6 \pm 0.9$ |
| Area 3–1–2        | Huntington | (10) | $80.4 \pm 4.7^*$    | $16.7 \pm 1.5$ | $19.1 \pm 1.8$ | $7.3 \pm 0.6$  | $14.2 \pm 0.7$ |
| Occipital         | Control    | (10) | $92.0 \pm 4.2$      | $9.7 \pm 0.9$  | $28.9 \pm 3.0$ | $10.0 \pm 1.1$ | $16.5 \pm 0.8$ |
| Area 17           | Huntington | (10) | $73.8 \pm 3.9^{**}$ | $10.0 \pm 1.2$ | $20.5 \pm 2.8$ | $9.3 \pm 2.0$  | $14.1 \pm 1.8$ |
| Inferior temporal | Control    | (10) | $117.0 \pm 12.5$    | $10.3 \pm 0.8$ | $22.6 \pm 2.5$ | $7.7 \pm 0.8$  | $11.5 \pm 0.9$ |
| Area 20           | Huntington | (10) | $95.7 \pm 4.7$      | $10.4 \pm 2.1$ | $21.4 \pm 1.5$ | $6.5 \pm 0.6$  | $9.1 \pm 0.4$  |
| Cingulate         | Control    | (10) | $119.0 \pm 10.9$    | $12.0 \pm 0.9$ | $15.9 \pm 0.7$ | $8.6 \pm 0.9$  | $16.2 \pm 2.2$ |
| Area 24           | Huntington | (10) | $101.0 \pm 4.0$     | $13.4 \pm 0.8$ | $20.1 \pm 0.9$ | $6.8 \pm 0.6$  | $10.2 \pm 0.7$ |
| Parahippocampal   | Control    | (7)  | $89.1 \pm 8.4$      | $10.7 \pm 1.2$ | $19.9 \pm 3.1$ | $8.0 \pm 0.9$  | $13.3 \pm 1.4$ |
| Area 28           | Huntington | (10) | $91.6 \pm 5.3$      | $12.0 \pm 0.9$ | $19.1 \pm 1.7$ | $7.5 \pm 0.8$  | $11.0 \pm 0.8$ |

Values are means  $\pm$  SEM. Areas refer to Brodmann's classification. The number of cases (grades 3 and 4) is in parentheses. \* $P < 0.05$ , \*\* $P < 0.02$ . GABA = gamma-aminobutyric acid.

groups in the pars compacta, but not in the pars reticulata of the substantia nigra (compacta: control,  $6.28 \pm 0.40$ ; HD 1 and 2,  $8.78 \pm 0.62$ ; HD 3 and 4,  $9.30 \pm 0.67$ ). Aspartate and taurine were unchanged in the substantia nigra. In other subcortical areas (Table 2), the only significant change among the amino acids was a 50%

TABLE 2. AMINO ACID LEVELS IN SUBCORTICAL AREAS (nmol/mg PROTEIN)

| Region                            | Group      |      | Glutamate        | GABA             | Aspartate      | Taurine        | Alanine        |
|-----------------------------------|------------|------|------------------|------------------|----------------|----------------|----------------|
| Hippocampus                       | Control    | (10) | $112.0 \pm 8.1$  | $10.4 \pm 1.1$   | $25.8 \pm 3.3$ | $12.7 \pm 1.2$ | $15.9 \pm 1.4$ |
|                                   | Huntington | (9)  | $110.0 \pm 6.4$  | $13.8 \pm 1.3$   | $20.5 \pm 2.7$ | $10.7 \pm 0.6$ | $14.9 \pm 1.6$ |
| Caudate                           | Control    | (6)  | $85.9 \pm 8.6$   | $9.8 \pm 0.9$    | $24.0 \pm 4.2$ | $6.9 \pm 0.7$  | $10.5 \pm 1.1$ |
|                                   | Huntington | (5)  | $107.0 \pm 14.7$ | $10.0 \pm 1.6$   | $24.9 \pm 2.6$ | $8.9 \pm 1.6$  | $12.8 \pm 1.4$ |
| Subthalamic nucleus               | Control    | (4)  | $56.8 \pm 2.2$   | $21.9 \pm 1.0$   | $24.7 \pm 3.5$ | $8.6 \pm 1.0$  | $13.2 \pm 2.1$ |
|                                   | Huntington | (8)  | $64.3 \pm 4.3$   | $18.0 \pm 3.1$   | $29.6 \pm 3.7$ | $6.5 \pm 0.5$  | $12.2 \pm 0.7$ |
| Ventrolateral nucleus of thalamus | Control    | (6)  | $96.6 \pm 7.2$   | $10.2 \pm 1.0$   | $36.3 \pm 3.8$ | $6.2 \pm 0.3$  | $15.6 \pm 0.9$ |
|                                   | Huntington | (6)  | $88.6 \pm 7.9$   | $10.3 \pm 1.7$   | $33.4 \pm 3.7$ | $6.0 \pm 0.7$  | $12.8 \pm 1.0$ |
| Anterior nucleus of thalamus      | Control    | (7)  | $88.7 \pm 6.8$   | $9.3 \pm 0.9$    | $20.9 \pm 0.9$ | $6.3 \pm 0.7$  | $13.6 \pm 1.6$ |
|                                   | Huntington | (6)  | $78.3 \pm 15.7$  | $14.0 \pm 1.8^*$ | $21.1 \pm 4.6$ | $6.9 \pm 1.2$  | $15.1 \pm 2.5$ |
| Dorsomedial nucleus of thalamus   | Control    | (7)  | $137.0 \pm 12.4$ | $11.8 \pm 1.3$   | $25.4 \pm 2.5$ | $7.1 \pm 0.7$  | $17.0 \pm 1.0$ |
|                                   | Huntington | (6)  | $111.0 \pm 14.1$ | $11.2 \pm 1.4$   | $22.3 \pm 3.3$ | $5.5 \pm 0.7$  | $15.2 \pm 1.0$ |

Values are means  $\pm$  SEM. The number of cases (grades 3 and 4) is in parentheses. \* $P < 0.05$ . GABA = gamma-aminobutyric acid.

increase in GABA in the anterior nucleus of the thalamus. Significant 16–20% decreases in glutamate concentration (Table 3) were found in Brodmann areas 3–1–2, 6, 9 and 17 of HD cortex, but other amino acids were unchanged. There was no correlation between amino acid levels and postmortem interval in any area.

TABLE 3. AMINO ACID LEVELS IN 9 CORTICAL AREAS (nmol/mg PROTEIN)

| Region            | Group      |      | Glutamate           | GABA           | Aspartate      | Taurine        | Alanine        |
|-------------------|------------|------|---------------------|----------------|----------------|----------------|----------------|
| Frontal           | Control    | (10) | $90.9 \pm 4.8$      | $9.1 \pm 0.7$  | $18.6 \pm 1.2$ | $6.9 \pm 0.5$  | $9.5 \pm 0.6$  |
| Area 9            | Huntington | (10) | $76.5 \pm 3.2^*$    | $10.2 \pm 0.8$ | $18.3 \pm 2.0$ | $5.7 \pm 0.4$  | $8.0 \pm 0.3$  |
| Frontal pole      | Control    | (5)  | $99.4 \pm 3.8$      | $13.0 \pm 1.8$ | $21.1 \pm 2.5$ | $7.8 \pm 1.0$  | $11.0 \pm 0.8$ |
| Area 10           | Huntington | (7)  | $94.8 \pm 5.6$      | $14.6 \pm 1.2$ | $20.7 \pm 1.2$ | $7.2 \pm 0.5$  | $9.8 \pm 0.6$  |
| Inferior frontal  | Control    | (5)  | $104.0 \pm 15.4$    | $10.5 \pm 1.1$ | $17.9 \pm 2.4$ | $6.4 \pm 0.8$  | $9.5 \pm 1.4$  |
| Area 11           | Huntington | (9)  | $100.0 \pm 8.1$     | $11.1 \pm 1.0$ | $20.4 \pm 2.2$ | $7.0 \pm 0.5$  | $8.7 \pm 0.8$  |
| Premotor          | Control    | (10) | $87.6 \pm 6.5$      | $8.9 \pm 0.9$  | $22.5 \pm 3.6$ | $7.6 \pm 0.6$  | $10.1 \pm 0.9$ |
| Area 6            | Huntington | (10) | $71.0 \pm 4.1^*$    | $10.8 \pm 0.8$ | $22.3 \pm 3.2$ | $6.4 \pm 0.7$  | $8.4 \pm 0.5$  |
| Postcentral       | Control    | (9)  | $96.3 \pm 5.8$      | $13.6 \pm 1.0$ | $18.9 \pm 1.0$ | $8.4 \pm 0.6$  | $15.6 \pm 0.9$ |
| Area 3–1–2        | Huntington | (10) | $80.4 \pm 4.7^*$    | $16.7 \pm 1.5$ | $19.1 \pm 1.8$ | $7.3 \pm 0.6$  | $14.2 \pm 0.7$ |
| Occipital         | Control    | (10) | $92.0 \pm 4.2$      | $9.7 \pm 0.9$  | $28.9 \pm 3.0$ | $10.0 \pm 1.1$ | $16.5 \pm 0.8$ |
| Area 17           | Huntington | (10) | $73.8 \pm 3.9^{**}$ | $10.0 \pm 1.2$ | $20.5 \pm 2.8$ | $9.3 \pm 2.0$  | $14.1 \pm 1.8$ |
| Inferior temporal | Control    | (10) | $117.0 \pm 12.5$    | $10.3 \pm 0.8$ | $22.6 \pm 2.5$ | $7.7 \pm 0.8$  | $11.5 \pm 0.9$ |
| Area 20           | Huntington | (10) | $95.7 \pm 4.7$      | $10.4 \pm 2.1$ | $21.4 \pm 1.5$ | $6.5 \pm 0.6$  | $9.1 \pm 0.4$  |
| Cingulate         | Control    | (10) | $119.0 \pm 10.9$    | $12.0 \pm 0.9$ | $15.9 \pm 0.7$ | $8.6 \pm 0.9$  | $16.2 \pm 2.2$ |
| Area 24           | Huntington | (10) | $101.0 \pm 4.0$     | $13.4 \pm 0.8$ | $20.1 \pm 0.9$ | $6.8 \pm 0.6$  | $10.2 \pm 0.7$ |
| Parahippocampal   | Control    | (7)  | $89.1 \pm 8.4$      | $10.7 \pm 1.2$ | $19.9 \pm 3.1$ | $8.0 \pm 0.9$  | $13.3 \pm 1.4$ |
| Area 28           | Huntington | (10) | $91.6 \pm 5.3$      | $12.0 \pm 0.9$ | $19.1 \pm 1.7$ | $7.5 \pm 0.8$  | $11.0 \pm 0.8$ |

Values are means  $\pm$  SEM. Areas refer to Brodmann's classification. The number of cases (grades 3 and 4) is in parentheses. \* $P < 0.05$ , \*\* $P < 0.02$ . GABA = gamma-aminobutyric acid.

Aspartate levels were now not different from the unlesioned side. In contrast, the glutamate deficit had become larger and was now 74% of the unlesioned side. Deficits of SPLI altered between the acute and chronic groups in a similar way to GABA and taurine, and levels were  $70 \pm 7\%$  of control ( $P < 0.01$ ) in the chronic group. SLI and NPYLI levels were again unchanged (SLI,  $84 \pm 4\%$ , NPYLI,  $86 \pm 10\%$ ).

Decortication reduced ipsilateral striatal glutamate and aspartate to 68% and 70% of contralateral levels respectively (fig. 4). No effect was seen on striatal GABA, but taurine was decreased significantly to 87% of contralateral levels. Combining QA and cortical lesions produced additive losses of striatal glutamate (49%) and aspartate (55%) 7 days postinjection. This contrasted with the situation 60 days postinjection, at which time decortication produced a further 14% loss of striatal aspartate but no additional loss of striatal glutamate (fig. 4). A supplementary decortication had no further effect on GABA and taurine beyond the changes seen with intrastriatal QA alone after either 7 days or 60 days. The standard errors of amino acid measurements on the control sides in all experiments were between 4–10%.

The acute and chronic groups both showed reductions in midbrain GABA and taurine. GABA levels were 52% and 61% of the contralateral side, and taurine levels 77% and 80% of the contralateral side, in the acute and chronic groups respectively. Other midbrain amino acids were unchanged by intrastriatal QA (fig. 5). Cortical levels of all the amino acids were unchanged by intrastriatal QA in both the acute and chronic groups (fig. 5).

## DISCUSSION

### *Postmortem studies*

An analysis of neurotransmitters in postmortem brain tissue has been central to the discovery of the differential susceptibility of neuronal populations in degenerative neurological illnesses (Beal and Martin, 1986b). In 1973, Perry *et al.* reported the first study of amino acids in HD brain. GABA concentrations were reduced in the caudate, putamen, globus pallidus, substantia nigra, and in occipital and temporal cortices. There were no significant changes in concentrations of glutamate, aspartate, or taurine. These findings were supported by McGeer *et al.* (1973) and Bird and Iversen (1974) who demonstrated reductions of the GABA synthesizing enzyme, glutamic acid decarboxylase in HD caudate, putamen, globus pallidus and substantia nigra. Subsequent larger studies controlled for agonal status have also confirmed this finding (Spokes, 1980; Wu *et al.*, 1979).

In the present study, we have replicated and extended the original postmortem studies on amino acids which showed deficits in GABAergic neuronal systems. GABA was decreased in the striatum, globus pallidus, and substantia nigra. In accordance with neuropathological grade, the GABA deficits were greater for the

severely affected (grades 3 and 4) group in all regions. The 54% GABA deficit in the caudate of the mildly affected (grades 1 and 2) group suggests that abnormalities in GABAergic neurons occur early in the disease process. There was a gradient of GABA deficit across the three striatal nuclei which matched the pattern of the pathological process. The caudate nucleus is involved first in the pathological process, and the nucleus accumbens is rarely affected until the later stages of the illness (Vonsattel *et al.*, 1985).

Levels of GABA in the basal ganglia are the highest in the brain and reflect the use of GABA as a neurotransmitter in striatal spiny neurons which project to the globus pallidus and substantia nigra (McGeer *et al.*, 1984). Some of the GABA neurons also contain the neuropeptides substance P, met-enkephalin, and dynorphin as neurotransmitters (Penny *et al.*, 1986). The neurochemical evidence strongly supports the pathological evidence that spiny neurons degenerate in HD. GABA is reduced in HD striatum, globus pallidus, and substantia nigra, all of which are target zones for spiny neuron axons. GABA deficits were greater in the external than the internal pallidum. The external segment is involved in the pathological process of the disease more than the internal (Bruyn *et al.*, 1979), and it is also the preferential projection of striatal neurons in which GABA and enkephalin are colocalized. Enkephalin levels are reduced in HD globus pallidus and substantia nigra (Emson *et al.*, 1980). The GABAergic projection from the striatum to the substantia nigra is topographically organized and mostly terminates in the pars reticulata (Carpenter, 1984). This is consistent with our finding larger GABA deficits in the pars reticulata, but a 56% drop was also seen in the pars compacta from the grades 3 and 4 group. Decreased GABA receptors in the ventral anterior thalamic nucleus have been reported for HD (Penney and Young, 1982), and it is interesting that we have found increased GABA levels in the anterior thalamus. Both these phenomena would reflect overactivity in the GABAergic pallidothalamic tract resulting from a loss of inhibitory striatopallidal input. GABA concentrations increase postmortem (Perry *et al.*, 1981), but our patient groups were matched for postmortem interval to obviate this potential source of error.

As a marker of neuronal populations, taurine has received little attention in the field of neurodegenerative disease. Taurine is released from rat striatal neurons upon depolarization (Girault *et al.*, 1986), and histological studies have shown uptake of labelled taurine and immunocytochemical staining of spiny striatal neurons (Clarke *et al.*, 1983; Campistron *et al.*, 1986). Excitotoxin lesions of the striatum with kainic acid result in taurine reductions in both striatum and substantia nigra (Nicklas *et al.*, 1979; Korf and Venema, 1983). These findings and our results with QA suggest that taurine may be contained within spiny striatal projection neurons. The relatively preserved concentrations of taurine that we found in HD striatum, globus pallidus, and substantia nigra would then represent an exception to the general rule that spiny striatal neurons are selectively affected in HD. However, the localization of taurine in the human striatum may be different from the rat. Striatal taurine concentrations are five-fold higher in the rat than in

the human, and the interpretation of concentration changes would be further complicated if taurine is localized to both aspiny and spiny neurons with differential susceptibilities to the HD process.

In the present study, we found decreased glutamate levels in the striatum and four cortical regions. The decreases were only significant for the grades 3 and 4 group, and it may have been heterogeneity of cases that prevented earlier authors from reliably detecting these changes. Perry did not find altered glutamate levels in his 1973 study, but a 30% reduction in caudate and putamen was reported later (Perry, 1982). Kremzner *et al.* (1979) have demonstrated a decreased glutamate concentration in HD frontal cortex.

There are at least three potential mechanisms which could account for reduced striatal concentrations of glutamate in HD. Aside from its neurotransmitter role, glutamate is a metabolic intermediate in both glia and neurons. Thus one possibility is that glutamate deficits merely reflect the loss of metabolic glutamate from nonglutamatergic neurons that degenerate in HD. Support for this possibility comes from studies (Nicklas *et al.*, 1979) that show that intrastriatal kainic acid decreases glutamate but does not reduce high affinity glutamate uptake, a marker for glutamatergic nerve terminals.

Glutamate and aspartate are putative neurotransmitters in the corticostriatal tract (Fonnum *et al.*, 1981). Reduced striatal glutamate therefore could reflect a primary degeneration of glutamatergic cortical neurons leading to a loss of striatal glutamatergic terminals or a secondary dying back of the corticostriatal tract due to striatal cell death and loss of postsynaptic contact. Whether the degeneration is primary or secondary, two other studies suggest that there is a loss of corticostriatal glutamatergic terminals in HD. Cross *et al.* (1986) proposed that large (60–72%) decreases in D-[<sup>3</sup>H]-aspartic acid binding to HD striatal membrane preparations are a consequence of loss of high affinity glutamate reuptake sites in a degenerating corticostriatal tract. Wong *et al.* (1982) reported a loss of ornithine aminotransferase activity in HD striatum, an enzyme thought to be relatively concentrated in glutamatergic nerve terminals. The activity of this enzyme is reduced by 37% in HD caudate and 49% in HD putamen.

Our results from the QA animal model demonstrate that a secondary degeneration of corticostriatal glutamatergic fibres can occur after a striatal lesion that replicates the neurochemical characteristics of HD (*see* Discussion of Animal Model). However, reduced cortical concentrations of glutamate did not accompany this degeneration. Thus our finding of reduced glutamate concentrations in HD cortex is more consistent with a primary degenerative process of the cortical neurons that use glutamate as a neurotransmitter. In addition, we found glutamate deficits in the postcentral gyrus and occipital cortex, two regions which do not project strongly to the striatum. Our data therefore point to a loss of cortical glutamatergic neurons in advanced grades of HD. This is consistent with pathological studies which have shown a neuronal loss in cortical layers III and V (Bruyn *et al.*, 1979), although other researchers have suggested that there is no appreciable

cortical abnormality (Dunlap, 1927). Further quantitative studies are needed to resolve this issue. If there is indeed a loss of glutamatergic cortical neurons in HD, this might contribute to the dementia which is characteristic of the disorder.

#### *Animal model*

The rationale for combining acute and chronic QA lesions with a decortication procedure was to determine whether decortication after a chronic QA lesion produced smaller reductions in striatal glutamate than decortication after an acute QA lesion. Such a result would be consistent with a secondary dying back of glutamatergic terminals in the chronic QA lesioned striatum, and would suggest that a similar phenomenon might contribute to decreased striatal glutamate levels in HD. Indeed this is what we found. The effect on striatal glutamate levels of supplementing an acute QA lesion with decortication was much the same as that for decortication alone: an additional drop of 32%. In contrast, the effect of supplementing a chronic QA lesion with decortication was an additional drop in glutamate of 7% which did not reach significance.

Decortication reduced striatal taurine levels by 13%, indicating that this amino acid might also be contained within the corticostriatal projection neurons. The changes in taurine levels when decortication was added to acute and chronic QA lesions followed the same pattern as those for glutamate. However, the additional 9% decrease in taurine between the acute plus decortication and acute groups was not significant.

Aspartate is also a marker for a set of corticostriatal fibres, and decortication alone reduced striatal levels to 70% of control. The effects on striatal aspartate of supplementing the acute and chronic QA groups with decortication were additional drops of 18% and 14%, respectively. Thus, the aspartatergic component of the corticostriatal tract appeared relatively spared in the chronic QA group. This distinction between glutamate and aspartate is consistent with our findings of reduced glutamate and unaltered aspartate in HD striatum.

The acute QA lesion group showed approximately 70% reductions in both striatal GABA and SPLI, and a 47% reduction in taurine. SLI and NPYLI concentrations were not significantly changed. These findings are consistent with our previous report (Beal *et al.*, 1986a) and indicate that while QA causes the death of spiny neurons, it spares the aspiny neurons which contain somatostatin and neuropeptide Y. Glutamate and aspartate were reduced by small amounts, probably representing loss of metabolic pools in degenerating neurons (Nicklas *et al.*, 1979).

In the chronic QA lesion group, many of the neurochemical deficits diminished in magnitude. The one exception was the glutamate deficit which went from 81% of control in the acute group to 74% of control in the chronic. GABA, taurine, and SPLI were all decreased to about 70% of control. Aspartate was not significantly reduced. These alterations between 7 and 60 days postinjection presumably reflect tissue shrinkage which has partially masked the neurochemical deficits. This proposal is supported by the lack of change in midbrain GABA and taurine levels

between the acute and chronic group. Surprisingly, concentrations of somatostatin and neuropeptide Y remained unaltered in the chronic group and did not increase as a consequence of shrinkage.

Comparing these results with those found in HD, we can make several observations. When injected into the striatum, QA can produce neurochemical changes similar to those in HD striatum. The reduction of GABA in the substantia nigra in HD is also replicated in the QA model. The major discrepancy is that taurine is significantly reduced in both striatum and midbrain after QA lesions, but it is unaltered throughout the basal ganglia in HD. As mentioned above, this lack of correspondence may reflect species differences. It would clearly be of interest to examine the distribution and morphologies of taurine-containing neurons in man and to examine the effects of QA striatal lesions in primates. Over time, QA striatal lesions appear to be accompanied by secondary changes in corticostriatal glutamatergic terminals. Although this process may well occur in HD and contribute to the glutamate deficit seen in HD striatum, our results with the QA model indicate that it probably does not account for the cortical glutamate deficits we have demonstrated. The latter change may reflect a primary process affecting the pyramidal neurons.

In conclusion, we have presented a detailed analysis of the levels of four amino acid neurotransmitters in 18 regions from neuropathologically graded cases of HD. In addition to extending previous findings of GABA abnormalities in the disease, we have demonstrated glutamate deficits in the striatum which may be due to a degeneration of the glutamatergic corticostriatal tract, and glutamate deficits in HD cortex which may be a primary feature of the disease process. We have confirmed the general applicability of the QA model of HD and have commented upon its implications.

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# VISUAL DYSFUNCTION IN PARKINSON'S DISEASE

## LOSS IN SPATIOTEMPORAL CONTRAST SENSITIVITY

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### SUMMARY

Flicker sensitivity and spatial contrast sensitivity (CS) were examined in a total of 99 patients with Parkinson's disease (PD). All patients were undergoing treatment with dopaminergic agents. Specific losses in sensitivity observed in PD were (1) a loss in flicker sensitivity which was most pronounced around the peak of the function (8 Hz) and (2) a loss near the peak of the spatial CS curve, often with no noticeable low frequency attenuation. Several PD patients affected by the 'on-off' syndrome were tested in both 'on' and 'off' phases, and the results show that the CS function switches in parallel with motor symptoms of the disease. These data suggest that not only is the visual system affected in PD, but that dopamine may have an essential role in receptive field organization in human vision.

### INTRODUCTION

In this paper, we show that both flicker sensitivity and spatial contrast vision are affected by Parkinson's disease (PD), and discuss the relevance of these findings to the physiology and pharmacology of the human visual system.

It is generally accepted that PD is primarily a motor disorder resulting from a deficiency of striatal dopamine. Other neurological defects affecting olfaction (Ansari and Johnson, 1975) and tactile sensation (Dinnerstein *et al.*, 1964) are also recognized, but have not yet been correlated with striatal dopaminergic activity. In our own studies, we have identified a significant number of patients with PD with defects in visual processing by employing the pattern visual evoked potential (PVEP) (Bodis-Wollner and Yahr, 1978). Other studies have also revealed that a number of patients with PD exhibit PVEP delays in either one or both eyes (Delwaide *et al.*, 1980; Gawel *et al.*, 1981; Kupersmith *et al.*, 1982; Sollazzo *et al.*, 1983). However, at least two studies (Hansch *et al.*, 1982; Ehle *et al.*, 1982) failed to demonstrate significant PVEP abnormalities. These negative data resulted from

using inappropriate methodology (Bodis-Wollner and Yahr, 1978; Bodis-Wollner, 1985). Recently, Tartaglione *et al.* (1985) and Onofrj *et al.* (1986b) described the effect of size of the stimulus element on the PVEP in PD and concluded that negative results arose when the PD patients were tested with pattern element sizes which were coarser than those used by most of the investigators who had demonstrated PVEP changes. Furthermore, a visual abnormality in PD may depend not only on the spatial but also on the temporal frequency of stimulation. For instance, we found that 4 Hz rather than 1 or 8 Hz modulation yielded the greatest number of PVEP abnormalities in PD when a 2.3 cycles/deg (cpd) sinusoidal grating was employed (Marx *et al.*, 1986). Apparently, visual changes in PD are dependent on both the spatial and temporal frequencies of stimulation.

During the last eight years, in addition to PVEP testing, we have studied flicker sensitivity and spatial contrast sensitivity (CS) of patients affected by PD. Kupersmith *et al.* (1982) reported abnormal CS in patients with PD using printed grating targets. Recently, Regan and Neima (1984) studied vision in PD using low contrast Snellen optotypes and reported that patients have defects for relatively large letters. Following an inquiry as to whether we had found spatial CS losses in PD (D. Regan, personal communication, 1984), we reevaluated our old data and performed additional studies. In general, we found that although the average magnitude of spatial CS losses may be small in a patient with PD, the shape of the complete CS function was changed in many patients with PD not only for temporal but also for spatial modulation. Some of these data have been reported in abstract form (Bodis-Wollner *et al.*, 1984). In the following, we shall briefly review the rationale of testing CS in patients whose acuity and visual fields may be normal.

Since their introduction over a decade ago, CS measurements have found increasing clinical application in the assessment of foveal vision in patients with neurological and ophthalmological disorders (Bodis-Wollner, 1972). With CS, a patient's ability to detect patterns of varying sizes rather than just the visual acuity (i.e. the smallest target size the observer can identify) can be quantified. Studies of patients with various neurological disorders (Bodis-Wollner and Diamond, 1976), have established that it is not possible to predict a patient's ability to detect coarse patterns on the basis of visual acuity (for review, see Bodis-Wollner and Camisa, 1980).

CS is usually established with sinusoidal gratings as test targets. These were originally introduced into animal and human physiological studies by F.W. Campbell, J. Robson and colleagues (Campbell and Green, 1965; Enroth-Cugell and Robson, 1966; Campbell and Robson, 1968) whose studies established that normal human CS function reflects both optical and neural attenuation; however, as opposed to a purely passive optical filter, the human CS curve shows a low spatial frequency decline. Low frequency CS attenuation is also observed in many levels of the visual system, including retinal ganglion cells, and its occurrence is attributed to the organization of centre and surround mechanisms of the receptive field (Enroth-Cugell and Robson, 1966). Pattern electroretinogram (PERG) measure-

ments also reveal a low spatial frequency decline (Hess and Baker, 1984). Recently, it has been established that the PERG reflects ganglion cell activity in primates (Maffei *et al.*, 1985). It is therefore likely that the low spatial frequency decline of the human CS curve also reflects the retinal input to the cortex of neurons with centre-surround organization.

Analogous to the spatial CS curve is the flicker sensitivity function. Detectability of sinusoidal flicker is plotted against temporal frequency and the resulting curve of the human temporal transfer function is named after de Lange (1958). The de Lange curve also shows low (temporal) frequency attenuation, analogous to the spatial curve. Finally, Robson (1966) and Kelly (1969) explored the detectability of various spatial frequencies at different rates of flicker. Their studies revealed that the normal human spatiotemporal CS is a function with a single peak. When presented as a three-dimensional surface plot, it shows low and high frequency attenuation in both spatial and temporal frequencies.

The studies we report here show that many patients with PD have an abnormality in both spatial and temporal vision. This is characterized as a specifically distorted shape of the CS function: the peak is flattened and low frequency attenuation is less apparent compared with normals. As we shall discuss, these data suggest that dopaminergic deficiency in PD affects the visual system and dopamine is likely to be one of the crucial neurotransmitters of receptive field tuning in human vision.

## METHODS

### *Observers*

*Patient selection.* A total of 99 patients with PD participated in at least one experiment of this study. All patients were undergoing treatment with dopaminergic agents. The patients were classified according to the clinical criteria of Hoehn and Yahr (1967): 90 of these patients with PD were classified as Stages II and III. However, we included 3 patients classified as Stage I and 6 patients classified as Stage IV since they satisfied the ophthalmological criteria which were a pupil diameter of at least 3 mm, visual acuity of 20/30+, clear ocular media, and no evidence of retinal pathology. The average age was 62.4 yrs with an SD of 11.7 yrs. Informed consent was obtained from all patients with PD before they participated in this study.

*Control subjects.* The control population consisted of 26 normal volunteers. All control observers underwent an ophthalmological examination and had to meet the same requirements described for the patients with PD. Only one eye of each control observer was tested for two reasons: (1) time constraint; since these persons served as normal subjects for all flicker and spatial contrast sensitivity measurements, a good deal of testing was necessary; and (2) statistical constraint, as in order to determine valid intervals based on the responses of normal observers, it is not appropriate to use more than one score per observer. When multiple scores per observer are employed, the resultant test statistic is biased. The mean age of the control observers was 47.9 yrs with SD of 11.8 yrs; 12 of the control observers were over 50 yrs of age and 6 of these were above 60 yrs. Nevertheless, there is a mean age difference of 14.5 yrs between the normal observers and the patients with PD. For this reason, we provide statistical analysis of the data of the patients which show that age alone cannot account for differences between responses in the normal observers and patients with PD. In addition, we present the CS functions of representative patients with PD whose ages are comparable to that of the mean of the control group.

*Flicker sensitivity*

A total of 41 patients with PD (82 eyes) were tested. Flicker sensitivity (spatial frequency = 0 cpd) measurements were made at 1, 2, 4, 8 and 16 Hz. Some of the patients, however, had problems with attention or suffered from fatigue, and could not perform all the experimental conditions or return for an additional testing session. Thus not all temporal frequencies were presented to all 41 patients with PD. To clarify any confusion, of these 41 patients the following numbers were tested at each of the flicker frequencies: 1 Hz = 6 patients (12 eyes); 2 Hz = 29 patients (58 eyes); 4 Hz = 30 patients (60 eyes); 8 Hz = 41 patients (82 eyes); 16 Hz = 29 patients (58 eyes).

For these and for all subsequent measurements, stimuli were generated on cathode-ray tubes (CRT). The screen of the CRT was always surrounded by a homogeneously illuminated field with a hue similar to that of the stimulus screen (its mean luminance was 0.2 log units lower than the screen). Monocular testing with natural pupils was always employed. The nontested eye was patched with gauze which transmitted light but blurred spatial detail. Viewing distance was always 1.44 m from the visual display.

A Tektronix 561 CRT served as the stimulus-generating display for the homogeneous field flicker. The flicker field was spatially uniform. Sinusoidal modulation was employed. Mean luminance was 10 cd/m<sup>2</sup>. Field size subtended 4° of visual angle. For each temporal frequency, flicker threshold was determined with the method of constant stimuli (MCS), in the manner previously described by Bodis-Wollner and Diamond (1976). The input to the CRT from the z axis was increased in successive steps of half a log unit until the observer indicated that the flicker was visible. We then assumed that the threshold occurred within this range of half a log unit (or 10 dB). For all threshold measurements, we will refer to zaxis attenuation in terms of decibels (dB), where 20 dB corresponds to 1 log unit (Wolkstein *et al.*, 1980). Once the 10 dB range was determined for a given temporal frequency, flicker stimuli which differed from each other by 2 dB (or 0.1 log unit) were presented to the observer. Following each presentation of the flicker, the observer was asked to indicate whether or not he or she detected the flicker. From these responses, the probability of detection was derived. We accepted 50% probability as the detection threshold. False negative and false positive responses were determined by random presentation of high and zero contrast stimuli (Bodis-Wollner and Diamond, 1976). Patients were excluded from the study when they responded positively to zero contrast stimuli or negatively to high contrast stimuli on at least 6 out of 20 presentations of a given stimulus condition.

In addition, we compared the threshold obtained by the MCS with the threshold obtained with a 2 alternative temporal forced choice (2 AFC) technique in each eye of 16 of these patients with PD. It is thought that the 2 AFC procedure produces a less biased threshold measurement in which decision criteria play a lesser role. The MSC was much easier to employ with the patients of this study. Many patients could not follow the instructions for the 2 AFC procedure.

The critical fusion frequency (CFF) was also determined in each eye of these 41 patients with PD using the same stimulus display. The CFF was determined by first decreasing and then increasing the temporal frequency of the 100% modulated flicker. After six passes each way, the mean value was defined as the CFF.

*Spatial contrast sensitivity*

A total of 10 patients with PD (19 eyes—1 eye was excluded as it did not meet our criteria) were tested. One patient (both eyes) had also performed the flicker sensitivity. As for the flicker sensitivity measurements, not all these patients were able to perform all of the stimulus conditions. Contrast sensitivity was measured to 1.2cpd in 10 patients (19 eyes), to 2.4cpd in 10 patients (19 eyes), to 4.8cpd in 9 patients (17 eyes), to 9.6cpd in 9 patients (17 eyes), to 14.4cpd in 7 patients (10 eyes) and to 19.2cpd in 7 patients (10 eyes). Although the number of patients tested for spatial CS is less than that tested for flicker sensitivity, we are confident of the reliability of these data. Six of these

patients were retested on 2 occasions and 2 patients were retested on 3 occasions, and their threshold variability did not exceed 3 dB.

Vertical gratings with sinusoidal luminance profiles were generated using the Tektronix 561 CRT. Viewing distance was 1.44 m and field size was 4° of visual angle. Spatial frequencies were tested from 1.2 to 19.2 cpd. The spatial CS curve was determined using on/off modulation at a rate of 1 Hz. Contrast sensitivity was assessed monocularly using the method of constant stimuli, already described for the flicker sensitivity measurements. In addition, we compared CS to counterphase and on/off modulation for a 1.2 cpd pattern modulated at 8 Hz in 6 of these 10 patients with PD (12 eyes). Counterphase (or pattern reversal) modulation refers to pattern presentation in which the light and dark elements of the pattern are alternately reversed, and on/off (or appearance/disappearance) modulation occurs when a pattern is presented and withdrawn, respectively, and the mean luminance is not changed (American Electroencephalographic Society, 1984).

#### *Spatiotemporal contrast sensitivity*

Eleven patients with PD (who had not yet been included in this study) were tested at 0.5, 1, 2, 4, 6 and 8 cpd using 1 and 8 Hz on/off modulation. A total of 17 eyes was tested: both eyes were examined in 6 of these 11 patients; in the other 5 patients, only 1 eye was tested. We report data from all 17 eyes in all conditions except for the 6 cpd grating presented at 1 Hz and at 8 Hz in which only 10 of the 17 eyes (or 7 of the 11 patients) were examined.

In this study, a special circuit Joyce Electronics CRT was used to present the vertical sinusoidal gratings. Mean luminance of the display was 100 cd/m<sup>2</sup>. The field size was 9° of visual angle. By employing a larger field size, we were able to present spatial frequencies as low as 0.5 cpd. Contrast thresholds were assessed for the spatiotemporal conditions using the method of constant stimuli.

We also examined 13 additional Patients with PD who were diagnosed as having the 'on-off' syndrome (Marsden and Parkes, 1976). Patients with this syndrome show practically no symptoms of the disease for several hours ('on' stage) after which they switch to disabling rigidity, akinesia or tremor ('off' stage). These patients are receiving regular doses of levodopa, and it is thought that 'on' and 'off' stages are due to high and then low dopamine responsiveness of postsynaptic dopamine receptors, respectively. It was very difficult to complete testing of all spatiotemporal (S-T) conditions in these patients in their 'on' periods as well as in their 'off' periods, and we were very fortunate in obtaining clearly separated 'on' and 'off' measurements in 6 patients. In the other 7 patients, their motor changes were either unpredictable or occurred too rapidly. The patients we were able to test in both 'on' and 'off' periods showed well marked clinical fluctuations between states of normal mobility or hyperkinesia and akinesia. They showed a 'positive' response to apomorphine given during an 'off' period (as described by Clough *et al.*, 1984), implying that their 'off' stages could be best explained as a 'supply-side' problem (i.e., a problem either in availability of dopamine or in the release of dopamine into the appropriate synaptic cleft).

We performed this study to investigate the role of dopamine on pattern vision by comparing 'on' vs 'off' CS responses in a particular patient. Contrast sensitivity was measured using the MCS. Only 5 spatial frequencies (0.5, 1, 2, 4, and 8 cpd) and 3 temporal frequencies (1, 4, and 8 Hz, on/off modulation) were employed. We elected to use the minimum amount of spatiotemporal conditions so that testing sessions would be relatively short. In this way, we were able to keep the 'on' and 'off' periods as separate. Three patients were tested on more than one occasion while in their 'on' states, and one patient was tested two separate times while in the 'off' state. Reproducibility of responses was very good (within 5 dB) in these 4 patients.

*Calibration of the stimuli.* Calibration procedures for the visual display and for the circuitry involved have been described in detail elsewhere (Bodis-Wollner and Hendley, 1979). In essence, a linear photocell was positioned behind two narrow slits (for the minimum aperture) to produce maximum output in front of a bright band of a static grating pattern. By counterphase modulating the grating pattern, we evaluated the peak and trough luminance without moving the photocell. To



ensure uniformity, additional measurements were made after positioning the slits and photocell at different points on the screen. The readings were comparable across the different screen positions. The results of this calibration were cross checked with values separately obtained over the 'dark' and 'bright' band using on-off modulation. Contrast was calculated with the formula  $C = (L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$  from the photocell's output voltage over a range of z axis input voltage to produce different contrast gratings. The voltage input versus contrast output values showed identical functions over the range of frequencies employed in this study. Only those stimulus parameters were used which remained within the linear range of the modulating circuit and visual display (80% contrast; 24 cpd).

## RESULTS

### *Flicker sensitivity*

The mean flicker sensitivity function of the normal observers, given our conditions of testing, peaked around 8 Hz with a low and high frequency roll-off (see fig. 1). Based on responses of the normal observers, means and SDs were calculated for flicker sensitivity at each temporal frequency. Flicker sensitivity of each patient was compared with the norm, and responses which fell 2 SDs below the normal mean for a given temporal frequency were considered abnormal for that rate of flicker. The breakdown of abnormalities of flicker sensitivity in PD is shown in Table 1. This shows that the greatest number of abnormal responses occurred with 8 Hz flicker (67% eyes were abnormal; 68.2% patients were abnormal) and with

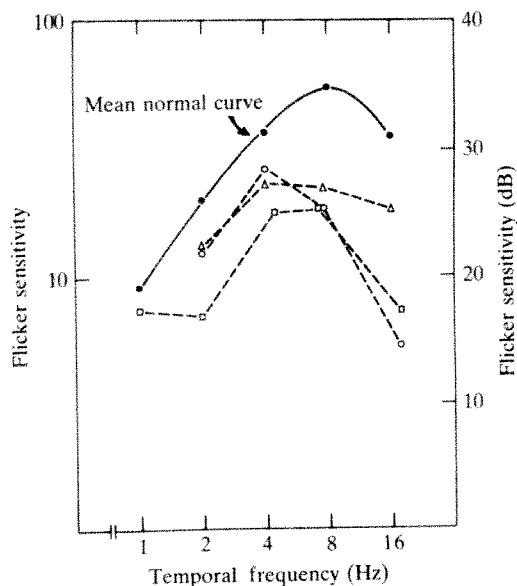


FIG. 1. Flicker sensitivity (1/flicker threshold) to a 4° field is shown as a function of temporal frequency for the mean normal curve (solid circles), for a 45-yr-old PD patient (open triangles), for a 56-yr-old PD patient (open squares), and for a 73-yr-old PD patient (open circles). Flicker sensitivity is also represented in terms of decibels (dB) on the right vertical axis.

TABLE 1. NUMBER (AND PERCENTAGE) OF PD EYES AND PD PATIENTS BELOW NORMAL LIMITS FOR FLICKER SENSITIVITY

|                                   | Flicker sensitivity (Hz) |                  |                  |                  |                  |
|-----------------------------------|--------------------------|------------------|------------------|------------------|------------------|
|                                   | 1                        | 2                | 4                | 8                | 16               |
| No. of eyes below normal limits   | 0/12<br>(0%)             | 23/58<br>(39.6%) | 20/60<br>(33.3%) | 55/82<br>(67%)   | 32/58<br>(55.1%) |
| No. of PD pts below normal limits | 0/6<br>(0%)              | 13/29<br>(44.8%) | 12/30<br>(40%)   | 28/41<br>(68.2%) | 18/29<br>(62%)   |

TABLE 2. FLICKER SENSITIVITY COMPARISONS WHICH WERE STATISTICALLY SIGNIFICANT USING McNEMAR'S TEST FOR CORRELATED PROPORTIONS

|                 |          |    |    |                         |                 |          |    |    |                         |
|-----------------|----------|----|----|-------------------------|-----------------|----------|----|----|-------------------------|
| 1.              |          |    |    |                         | 6.              |          |    |    |                         |
| 2 Hz            |          |    |    |                         | 16 Hz           |          |    |    |                         |
| Abnormal Normal |          |    |    |                         | Abnormal Normal |          |    |    |                         |
| 1 Hz            | Abnormal | 0  | 0  | 0                       | 2 Hz            | Abnormal | 21 | 2  | 23                      |
|                 | Normal   | 12 | 0  | 12                      |                 | Normal   | 11 | 24 | 35                      |
|                 |          | 12 | 0  | 12 eyes                 |                 |          | 32 | 26 | 58 eyes                 |
|                 |          |    |    | $\chi^2_1 = 12.00^{**}$ |                 |          |    |    | $\chi^2_1 = 6.23^*$     |
| 2.              |          |    |    |                         | 7.              |          |    |    |                         |
| 4 Hz            |          |    |    |                         | 8 Hz            |          |    |    |                         |
| Abnormal Normal |          |    |    |                         | Abnormal Normal |          |    |    |                         |
| 1 Hz            | Abnormal | 0  | 0  | 0                       | 4 Hz            | Abnormal | 20 | 0  | 20                      |
|                 | Normal   | 11 | 1  | 12                      |                 | Normal   | 19 | 21 | 40                      |
|                 |          | 12 | 1  | 12 eyes                 |                 |          | 39 | 21 | 60 eyes                 |
|                 |          |    |    | $\chi^2_1 = 11.00^{**}$ |                 |          |    |    | $\chi^2_1 = 19.00^{**}$ |
| 3.              |          |    |    |                         | 8.              |          |    |    |                         |
| 8 Hz            |          |    |    |                         | 16 Hz           |          |    |    |                         |
| Abnormal Normal |          |    |    |                         | Abnormal Normal |          |    |    |                         |
| 1 Hz            | Abnormal | 0  | 0  | 0                       | 4 Hz            | Abnormal | 18 | 2  | 20                      |
|                 | Normal   | 11 | 1  | 12                      |                 | Normal   | 14 | 24 | 38                      |
|                 |          | 11 | 1  | 12 eyes                 |                 |          | 32 | 26 | 58 eyes                 |
|                 |          |    |    | $\chi^2_1 = 11.00^{**}$ |                 |          |    |    | $\chi^2_1 = 9.00^{**}$  |
| 4.              |          |    |    |                         | 9.              |          |    |    |                         |
| 16 Hz           |          |    |    |                         | 16 Hz           |          |    |    |                         |
| Abnormal Normal |          |    |    |                         | Abnormal Normal |          |    |    |                         |
| 1 Hz            | Abnormal | 0  | 0  | 0                       | 1 Hz            | Abnormal | 30 | 11 | 41                      |
|                 | Normal   | 12 | 0  | 12                      |                 | Normal   | 2  | 17 | 19                      |
|                 |          | 12 | 0  | 12 eyes                 |                 |          | 32 | 28 | 60 eyes                 |
|                 |          |    |    | $\chi^2_1 = 12.00^{**}$ |                 |          |    |    | $\chi^2_1 = 6.23^*$     |
| 5.              |          |    |    |                         |                 |          |    |    |                         |
| 8 Hz            |          |    |    |                         |                 |          |    |    |                         |
| Abnormal Normal |          |    |    |                         |                 |          |    |    |                         |
| 2 Hz            | Abnormal | 22 | 7  | 29                      |                 |          |    |    |                         |
|                 | Normal   | 17 | 12 | 29                      |                 |          |    |    |                         |
|                 |          | 39 | 19 | 58 eyes                 |                 |          |    |    |                         |
|                 |          |    |    | $\chi^2_1 = 4.166^*$    |                 |          |    |    |                         |

\*  $P < 0.05$ , \*\*  $P < 0.01$ .

16 Hz flicker (55.1% eyes were abnormal; 62% patients were abnormal). To determine statistically the difference in abnormality rates to the different temporal frequencies, McNemar's test for correlated proportions was performed on the data from the patients. The data were categorized as normal or abnormal and put into  $2 \times 2$  tables, each table comparing abnormality rates to two of the temporal frequencies employed in this study. The resulting test statistic for each  $2 \times 2$  table yielded a  $\chi^2$  distribution with 1 df. The null hypothesis was that there is no difference in normality rates to flicker sensitivity to the 2 temporal frequencies for the patients with PD in the present study. All statistically significant comparisons are shown in Table 2. Several interesting results emerged from this analysis: (1) flicker sensitivity at 1 Hz yields a higher normality rate in PD than does flicker sensitivity at 2, 4, 8, or 16 Hz (*see* comparisons 1–4); (2) significantly higher abnormality rates occurred with 8 and 16 Hz than with 1, 2, or 4 Hz (comparisons 5–8); and (3) when comparing flicker sensitivity to 8 vs 16 Hz, we found a significantly higher abnormality rate with 8 than with 16 Hz in these patients (comparison 9). Thus our data show that sensitivity to 8 Hz (the peak of the normal flicker sensitivity function) is the temporal frequency most severely affected in PD. Yet the normality rate in PD remains at 100% for flicker sensitivity at 1 Hz. It appears that both the shape as well as the peak of the flicker sensitivity function are affected in PD. This suggestion is well represented in fig. 1 in which flicker sensitivity of 3 patients with PD is shown relative to the mean normal curve. None of the patient curves shows a clear peak at 8 Hz. In addition, the age difference between the control observers and the patients does not appear to be a primary cause of decreased sensitivity in these PD patients. For instance, flicker sensitivity of the 73-yr-old patient is comparable to (and, at certain temporal rates, actually higher than) the sensitivity functions of younger patients with PD.

The age difference is not a matter that should be lightly dismissed. To exclude the possibility that perhaps ageing was responsible for our results, we examined the relationship between flicker sensitivity and age of the patients of our study. A scatterplot was drawn with the age of the patients on the abscissa and flicker sensitivity measurement at 8 Hz on the ordinate (*see* fig. 2). We chose the flicker rate of 8 Hz since this temporal frequency produced the highest abnormality yield in the patients with PD. Pearson's correlation coefficient was then calculated from these data. Separate correlation coefficients were determined for the right and left eyes, as we did not want to bias the statistics by including more than one entry per patient. Neither correlation coefficient reached statistical significance (right eye:  $r = -0.289$ ,  $df = 39$ ; left eye:  $r = -0.267$ ,  $df = 39$ ). Thus flicker sensitivity did not change systematically with increasing age in these patients. The difference in mean age between the patients and control observers cannot adequately explain the abnormalities observed in the flicker sensitivity of these patients with PD.

In 16 of the patients, flicker sensitivity was compared at 2, 4, 8, and 16 Hz using both the method of constant stimuli and the bias-free method of 2 AFC. We compared these two psychophysical methods to assess whether or not the non-

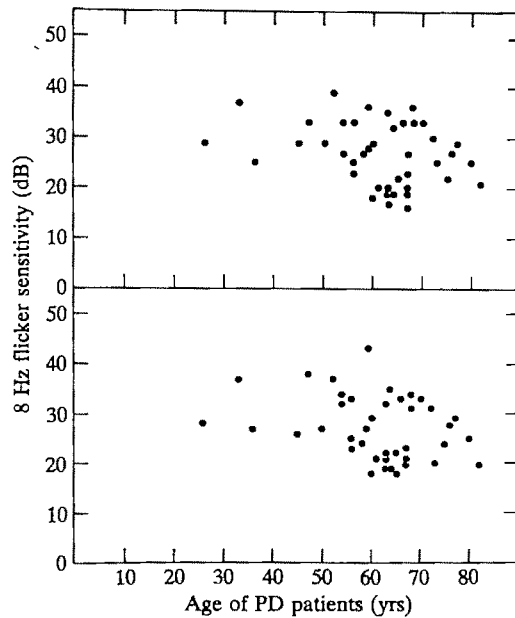


FIG. 2. Flicker sensitivity to 8 Hz flicker is shown as a function of age of individual eyes of the PD patients. Pearson's correlation coefficient is  $-0.289$  for the right eye (top of fig.), and  $-0.267$  for the left eye (bottom of fig.), and does not reach statistical significance for either eye.

biased 2 AFC performance reproduces the temporal frequency-specific dysfunction revealed by the MSC. The 2 AFC technique proved to be too difficult for some of the patients. However, of the patients with PD in which both 2 AFC and MCS thresholds were obtained, little difference was found in sensitivity using either method. Hence we concluded that 'bias' plays a minimal, if any, role in determining flicker sensitivity in PD. The data comparing 2 AFC and MCS thresholds will be presented in a separate paper.

We also assessed the critical flicker fusion frequency (CFF) in the PD patients. In the normal observers, the mean CFF was 42 Hz with a SD of 4.2 Hz. The CFF value from each eye of each PD patient was compared with the norm, and responses which fell 2 SDs below the normal mean (this value was truncated to 33 Hz) were counted as abnormal. The CFF was below normal limits in 24 out of the 41 patients (58.5%). Looked at another way, 51.2% of the eyes of these patients with PD were abnormal (42/82 abnormal eyes).

### *Spatial contrast sensitivity*

The mean spatial contrast sensitivity function of the normal observers is presented in fig. 3. Based on the normal responses, means and SDs were calculated for spatial CS for each spatial frequency. The spatial CS values of each eye of the patients were compared with the norm, and responses which fell 2 SDs below the

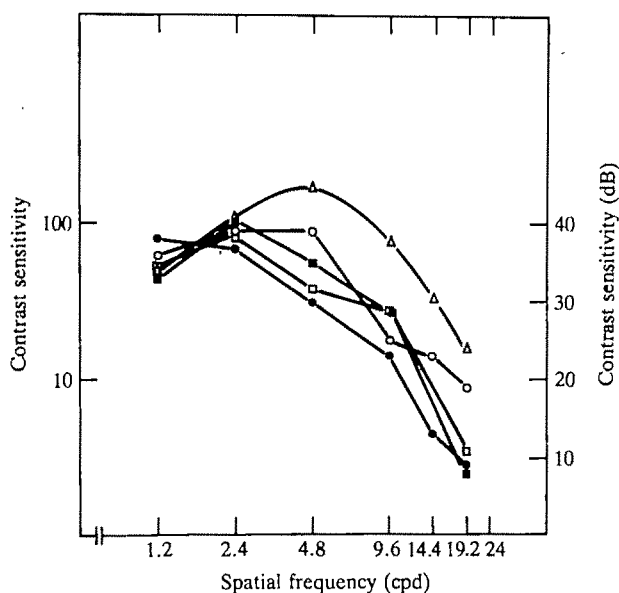


FIG. 3. Spatial contrast (1/contrast threshold) to a 4° field is presented as a function of spatial frequency for the mean normal curve (open triangles) for each eye of a 60-yr-old PD patient (right eye as open circle, left eye as closed circle), and for each eye of a 51-yr-old PD patient (right eye as an open square, left eye as a closed square). Spatial contrast sensitivity is also shown in terms of decibels (dB) on the right vertical axis.

normal mean for a given spatial frequency were counted as abnormal for that grating. The breakdown of abnormal CS in the patients with PD is shown in Table 3.

All the patients with PD exhibited losses in CS for the spatial frequency of 4.8 cpd, which is the peak of the normal CS curve (*see* Table 3). In most instances, contrast sensitivity was also below normal limits for spatial frequencies above 4.8 cpd. Noticeably, there were few losses in CS for spatial frequencies below 4.8 cpd: 5% of eyes were abnormal for 1.2 cpd and 15.7% of eyes were abnormal for 2.4 cpd. To determine statistically whether differences in normality rates occurred between the different spatial frequencies, McNemar's test was performed on the data of the PD patients in the manner previously described for the flicker sensitivity data. Statistically significant comparisons are presented in Table 4. Comparisons of 1.2 cpd vs 4.8, 9.6, 14.4, and 19.2 cpd (comparisons 1–4) were all statistically significant. In addition, comparisons of 2.4 cpd vs 4.8, 9.6, 14.4, and 19.2 cpd (comparisons 5–8) were all statistically significant. These results indicate that normality rates were higher for 1.2 cpd and for 2.4 cpd than for spatial frequencies of 4.8 cpd and above in these patients with PD. There were no significant differences in normality rates between the combinations of spatial frequencies of 4.8 cpd and above, suggesting that these spatial frequencies all yielded abnormal contrast sensitivity scores.

The data from 2 patients with PD are shown with the mean CS function of the normal observers in fig. 3. We selected 2 patients since their ages are close to that

TABLE 3. NUMBER (AND PERCENTAGE) OF PD EYES AND PD PATIENTS BELOW NORMAL LIMITS FOR SPATIAL CONTRAST SENSITIVITY

|                                   | <i>Spatial frequency (cpd)</i> |                 |                 |                  |               |                |
|-----------------------------------|--------------------------------|-----------------|-----------------|------------------|---------------|----------------|
|                                   | 1.2                            | 2.4             | 4.8             | 9.6              | 14.4          | 19.2           |
| No. of eyes below normal limits   | 1/19<br>(5%)                   | 3/19<br>(15.7%) | 17/17<br>(100%) | 15/17<br>(88.2%) | 9/10<br>(90%) | 7/10<br>(70%)  |
| No. of PD pts below normal limits | 1/10<br>(10%)                  | 2/10<br>(20%)   | 9/9<br>(100%)   | 8/9<br>(88.8%)   | 7/7<br>(100%) | 6/7<br>(85.7%) |

of the normal observers (normal mean age 47.9 yrs). There is a lack of spatial frequency tuning around 4.8 cpd and an apparent absence of attenuation to the lower spatial frequency gratings in the CS functions of the PD patients.

We also assessed the interocular difference (in dB) for each spatial frequency in 9 of these 10 patients with PD. In the normal observers, we found that the average interocular difference was 2.5 dB with a SD of 0.5 dB for spatial frequencies from 1.2 to 24 cpd. The interocular differences for each spatial frequency of each PD

TABLE 4. SPATIAL CONTRAST SENSITIVITY COMPARISONS WHICH WERE STATISTICALLY SIGNIFICANT USING McNEMAR'S TEST FOR CORRELATED PROPORTIONS.

|                 |          |    |   |                         |                 |          |    |   |                         |
|-----------------|----------|----|---|-------------------------|-----------------|----------|----|---|-------------------------|
| 1.              |          |    |   |                         | 5.              |          |    |   |                         |
| 4.8 cpd         |          |    |   |                         | 4.8 cpd         |          |    |   |                         |
| Abnormal Normal |          |    |   |                         | Abnormal Normal |          |    |   |                         |
| 1.2 cpd         | Abnormal | 0  | 0 | 0                       | 2.4 cpd         | Abnormal | 3  | 0 | 3                       |
|                 | Normal   | 17 | 0 | 17                      |                 | Normal   | 13 | 0 | 13                      |
|                 |          | 17 | 0 | 17 eyes                 |                 |          | 16 | 0 | 16 eyes                 |
|                 |          |    |   | $\chi^2_1 = 17.00^{**}$ |                 |          |    |   | $\chi^2_1 = 13.00^{**}$ |
| 2.              |          |    |   |                         | 6.              |          |    |   |                         |
| 9.6 cpd         |          |    |   |                         | 9.6 cpd         |          |    |   |                         |
| Abnormal Normal |          |    |   |                         | Abnormal Normal |          |    |   |                         |
| 1.2 cpd         | Abnormal | 0  | 0 | 0                       | 2.4 cpd         | Abnormal | 3  | 0 | 3                       |
|                 | Normal   | 15 | 2 | 17                      |                 | Normal   | 11 | 2 | 13                      |
|                 |          | 15 | 2 | 17 eyes                 |                 |          | 14 | 2 | 16 eyes                 |
|                 |          |    |   | $\chi^2_1 = 15.00^{**}$ |                 |          |    |   | $\chi^2_1 = 11.00^{**}$ |
| 3.              |          |    |   |                         | 7.              |          |    |   |                         |
| 14.4 cpd        |          |    |   |                         | 14.4 cpd        |          |    |   |                         |
| Abnormal Normal |          |    |   |                         | Abnormal Normal |          |    |   |                         |
| 1.2 cpd         | Abnormal | 0  | 0 | 0                       | 2.4 cpd         | Abnormal | 2  | 0 | 2                       |
|                 | Normal   | 9  | 1 | 10                      |                 | Normal   | 7  | 0 | 7                       |
|                 |          | 9  | 1 | 10 eyes                 |                 |          | 9  | 0 | 9 eyes                  |
|                 |          |    |   | $\chi^2_1 = 9.00^{**}$  |                 |          |    |   | $\chi^2_1 = 7.00^{**}$  |
| 4.              |          |    |   |                         | 8.              |          |    |   |                         |
| 19.2 cpd        |          |    |   |                         | 19.2 cpd        |          |    |   |                         |
| Abnormal Normal |          |    |   |                         | Abnormal Normal |          |    |   |                         |
| 1.2 cpd         | Abnormal | 0  | 0 | 0                       | 2.4 cpd         | Abnormal | 1  | 0 | 1                       |
|                 | Normal   | 7  | 3 | 10                      |                 | Normal   | 5  | 3 | 8                       |
|                 |          | 7  | 3 | 10 eyes                 |                 |          | 6  | 3 | 9 eyes                  |
|                 |          |    |   | $\chi^2_1 = 7.00^{**}$  |                 |          |    |   | $\chi^2_1 = 5.00^*$     |

\*  $P < 0.05$ , \*\*  $P < 0.01$ .

patient were compared with the norm, and responses above 3.5 dB (i.e., 2 SDs above the normal mean) were counted as abnormal. Abnormal interocular differences were found in 0/9 patients for the 1.2 cpd grating, in 1/9 patients for the 2.4 cpd grating, in 5/8 patients for the 4.8 cpd grating, in 3/8 patients for the 9.6 cpd grating, in 2/3 patients for the 14.4 cpd grating, in 1/2 patients for the 19.2 cpd grating, and in 1/1 patient for the 24 cpd grating. In summary, except in 1 patient, interocular differences fell within normal limits for spatial frequencies of 2.4 cpd or below; yet abnormal interocular differences were observed for spatial frequencies above 2.4 cpd. The fact that the same patients showed little interocular difference at 2.4 cpd with an abnormal difference at 4.6 cpd, suggests that both absolute CS and interocular differences arise from pathology having a significant uniocular or asymmetric effect. Furthermore, the pathology affects the detectability of only a portion of the spatial frequency spectrum (the peak of the CS function, 4.8 cpd, and the higher spatial frequencies). These data are consistent with recently reported VEP results which show that a visual abnormality becomes apparent in PD when patterns above 2 cpd are used (Tartaglione *et al.*, 1985; Onofrij *et al.*, 1986b).

We also examined differences in CS in PD when counterphase, instead of on/off temporal modulation, is employed. It is well known that in the normal eye, sensitivity to low spatial frequency patterns increases by a factor of 2 (6 dB) when the pattern is presented in a counterphase rather than on/off manner (Kulikowski and Tolhurst, 1973). In this experiment, a 1.2 cpd sinusoidal grating was square-wave modulated at a rate of 8 Hz. These responses were measured in only 10 of the 26 normal observers (20 eyes). The mean age of this group of normal observers was 58.1 yrs. In these normal observers, the mean sensitivity increase from on/off-to-counterphase modulation was 7.55 dB with a SD of 3.74 dB. The normal limits, derived as 2 SDs above and 2 SDs below the mean, were 0–15 dB. In 6 patients with PD (12 eyes), the mean sensitivity increase equalled 4.5 dB, and the range of responses was from 1 to 10 dB. Thus despite the small number of eyes tested for this comparison, we found no evidence that abnormal increases of sensitivity occur in PD. If counterphase modulation with 'flicker' detection and on/off modulation with 'pattern' detection are associated (based on Kulikowski and Tolhurst, 1973), it follows that the pathology affecting spatial contrast detection in PD may occur before the segregation of the two pathways postulated to mediate the detection of flicker and pattern (or alternately, that the pathology may involve both). A different type of response trend has been reported in glaucoma. Regan and Neima (1984) demonstrated a dissociation between pattern and flicker detection in most glaucoma patients. In those glaucomatous eyes, one threshold could be abnormal while the other was clearly within normal limits.

#### *Spatiotemporal (S-T) contrast sensitivity*

In normal observers, sensitivity decreases for low spatial frequencies with low rates of temporal modulation, and an increase in CS occurs when the rate of

temporal modulation is increased (Robson, 1966). Our normal data, shown in fig. 4, are consistent with those previously reported in the literature. Also in fig. 4, we present data from 2 patients with PD. As for spatial contrast sensitivity, we selected these patients to illustrate that the age differences between the control observers and the patients cannot account for our results. Note that CS is attenuated in the 49-yr-old patient, an age similar to the average normal data. Moreover, we show

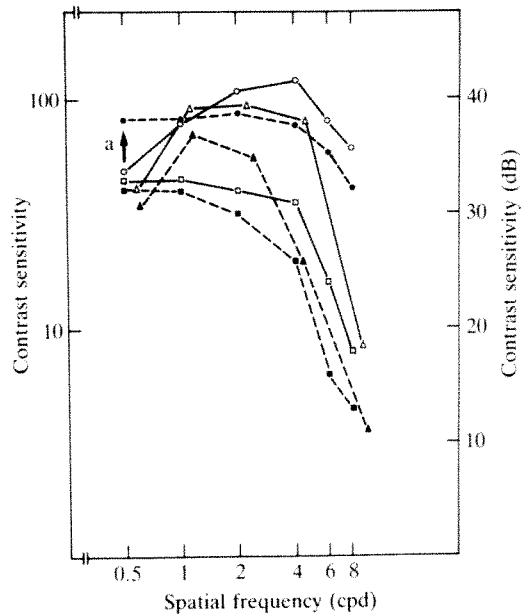


FIG. 4. Spatiotemporal contrast sensitivity to a  $9^\circ$  field is shown for 5 spatial frequencies which were on/off modulated using temporal frequencies of 1 Hz (solid lines) or 8 Hz (interrupted lines). Contrast sensitivity ( $1/\text{contrast threshold}$ ) is shown on the left vertical axis and contrast sensitivity is measured in decibels (dB) on the right vertical axis. The mean normal curves are represented by circles. The 1 and 8 Hz functions of a 49-yr-old PD patient are represented by squares. The 1 and 8 Hz functions of a 69-yr-old PD patient are represented by triangles. 'Sensitivity gain' is labelled 'a' (indicated by an upward vertical arrow), and refers to the increase of contrast sensitivity which occurs to the 0.5 cpd grating when the rate of temporal modulation is increased from 1 to 8 Hz (*see text*). Notice that age does not determine the 'parkinsonian' type of CS defects illustrated in this figure, as explained in the text.

that CS is higher for the 69-yr-old patient than for the 49-yr-old patient. This figure also points to a variability among some patients in their contrast sensitivity data, in that the peak is attenuated and there is no low frequency decline in the younger patient while, in the older patient, the peak is also attenuated and broadened although a low frequency decline is still evident. Nevertheless, if we take the ratio of contrast sensitivity at the peak of the function to contrast sensitivity to the 0.5 cpd grating, the results also indicate that in the older patient there is a weakening of low frequency attenuation. Alternatively, the results obtained in the older patient



(and also evident in some of the other patients with PD) could be viewed as a shift of the entire CS curve, down and to the left, as discussed later.

Fig. 4 shows that differences between 1 vs 8 Hz CS at low spatial frequencies are not pronounced in PD. In normal observers, we refer to the increase of CS which occurs to the 0.5 cpd grating when the rate of temporal modulation is increased from 1 Hz to 8 Hz as the 'sensitivity gain' (represented as 'a' in the figure). We found the average sensitivity gain to be +4.8 dB with an SD of 2.1 dB. We compared the sensitivity gain of the 17 PD eyes with the norm, and responses which were 2 SDs below the normal mean were counted as abnormal. Eight of the 17 eyes (or 6/11 patients with PD) were abnormal. Five of these abnormal eyes had *negative* sensitivity scores, indicating that CS for 1 Hz modulation was actually *higher* than CS for 8 Hz modulation.

The 1 Hz and 8 Hz CS values to the different spatial frequencies in each patient were compared with the norm, and responses which fell 2 SDs below the normal mean for a given spatiotemporal condition were counted as abnormal. The breakdown of abnormal spatiotemporal CS in the patients with PD is shown in Table 5, which shows that abnormal responses to spatial frequencies of 2 cpd and above occurred equally often for 1 Hz and 8 Hz. To determine whether abnormality rates in these data were statistically different, McNemar's test was performed. The abnormality rates were significantly different for comparisons between 1 vs 8 Hz CS for the 0.5 cpd grating and for the 1 cpd grating (*see* Table 6). However, comparisons between spatial frequencies of 2 cpd and above failed to reach statistical significance. Thus the greatest number of abnormal responses occurred with 8 Hz modulation of the low spatial frequency gratings, a result also suggested by our examination of 'sensitivity gain' at 0.5 cpd.

To assess CS to 0.5 cpd and 8 Hz in more detail, we measured this response in a total of 25 additional patients with PD (50 eyes). Pearson's correlation coefficient

TABLE 5. BREAKDOWN OF ABNORMAL SPATIOTEMPORAL CS IN THE PD PATIENTS

|     | 1 Hz                         |                                  | 8 Hz                         |                                  |
|-----|------------------------------|----------------------------------|------------------------------|----------------------------------|
|     | No. of PD eyes<br>below norm | No. of PD patients<br>below norm | No. of PD eyes<br>below norm | No. of PD patients<br>below norm |
| cpd |                              |                                  |                              |                                  |
| 0.5 | 6/17<br>(35.3%)              | 4/11<br>(36.3%)                  | 13/17<br>(76.4%)             | 8/11<br>(72.7%)                  |
| 1.0 | 5/17<br>(29.4%)              | 4/11<br>(36.3%)                  | 9/17<br>(53%)                | 5/11<br>(45.4%)                  |
| 2.0 | 12/17<br>(70.5%)             | 8/11<br>(72.7%)                  | 10/17<br>(59%)               | 8/11<br>(72.7%)                  |
| 4.0 | 12/17<br>(70.5%)             | 8/11<br>(72.7%)                  | 13/17<br>(76.4%)             | 9/11<br>(81.8%)                  |
| 6.0 | 4/10<br>(40%)                | 3/7<br>(42.8%)                   | 4/10<br>(40%)                | 3/7<br>(42.8%)                   |
| 8.0 | 6/17<br>(35.3%)              | 5/11<br>(45.4%)                  | 5/17<br>(29.4%)              | 5/11<br>(45.4%)                  |

TABLE 6. SPATIOTEMPORAL CS COMPARISONS WHICH WERE STATISTICALLY SIGNIFICANT USING McNEMAR'S TEST FOR CORRELATED PROPORTIONS

| 1.             |          | 8 Hz, 0.5cpd           |        |         |
|----------------|----------|------------------------|--------|---------|
|                |          | Abnormal               | Normal |         |
| 1 Hz<br>0.5cpd | Abnormal | 6                      | 0      | 6       |
|                | Normal   | 7                      | 4      | 11      |
|                |          | 13                     | 4      | 17 eyes |
|                |          | $\chi^2_1 = 7.00^{**}$ |        |         |

| 2.             |          | 8 Hz, 1.0cpd        |        |         |
|----------------|----------|---------------------|--------|---------|
|                |          | Abnormal            | Normal |         |
| 1 Hz<br>1.0cpd | Abnormal | 5                   | 0      | 5       |
|                | Normal   | 4                   | 8      | 12      |
|                |          | 9                   | 8      | 17 eyes |
|                |          | $\chi^2_1 = 4.00^*$ |        |         |

\*  $P < 0.05$ , \*\*  $P < 0.01$ .

was then calculated from these data with patient age as the x variable and the CS value as the y variable. Neither the correlation coefficient for the right eye nor that for the left reached statistical significance (right eye:  $r = 0.030$ ,  $df = 23$ ; left eye:  $r = -0.276$ ,  $df = 23$ ). CS did not vary significantly with increasing age in these patients with PD. Clearly, age is not the major determinant of the CS loss in PD.

All our data were obtained in patients receiving dopamine precursor therapy on a regular basis. To evaluate the presumed effect of dopamine on pattern vision, we examined 13 patients with the 'on-off' syndrome. Clear differences in S-T CS were observed in 'on' vs 'off' stages in 6 patients. These 6 (out of the 13) patients showed sufficient segregation in time of 'on' and 'off' stages, and a stability of their psychological responses during each stage. Stability was judged by the slope of the psychometric function obtained for each threshold measurement and by repeating selected spatial frequencies at the end of each session.

In normal observers, the S-T surface is a function with a single peak around 4 cpd. In general, the S-T surfaces of these PD patients tended to show less height than that of the normal surface (i.e., there is a generalized reduction in sensitivity). However, our results clearly show the importance of considering visual sensitivity separately in 'on' and 'off' states. We found that not only the height but, most importantly, the shape of the S-T surface changes between 'on' and 'off' states. Spatiotemporal surfaces were derived for 6 patients (one eye only in 5 patients, both eyes in the sixth patient). Of the 7 patient eyes, 5 showed an *increase* in CS to 0.5 cpd at 1 Hz in the 'off' vs the 'on' condition, while CS in the other 2 eyes did not change. At 4 cpd and 1 Hz, 5 eyes showed an increase and 2 eyes showed a minor ( $-1$  dB) decrease in the 'on' condition. At 4 cpd and 4 Hz, 5 eyes showed

an increase near the peak of the S-T surface and 2 eyes did not change when the 'on' state was compared with the 'off' state. Thus CS is higher at the lower spatial frequency in the 'off' condition, and CS is higher at the peak of the spatial frequency function in the 'on' condition—in the same eye of a patient with PD. Spatiotemporal surfaces of one patient with PD are shown in fig. 5. The S-T surface in the 'on' state shows a peak as well as a relative attenuation to combinations of low spatial frequencies and low temporal frequencies. The S-T surface in the 'off' state resembles a plateau and does not present a discernible peak. As mentioned before, it is thought that 'on' and 'off' states represent 'high' versus 'low' dopaminergic activity in patients with PD who are undergoing treatment (Marsden and Parkes, 1976; Clough *et al.*, 1984). Therefore, by obtaining a difference in the CS function between the 'on' and 'off' states, insight may be gained into the effect of dopamine

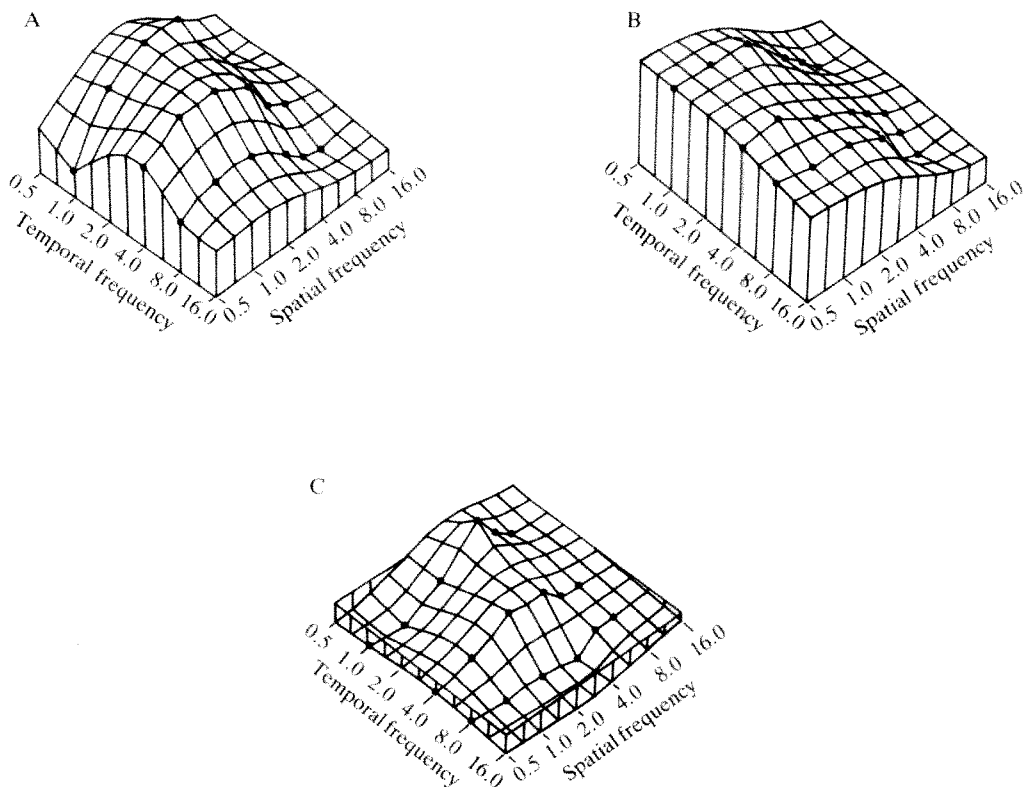


FIG. 5. Spatiotemporal contrast sensitivity to a  $9^\circ$  field is shown for 6 spatial frequencies and 6 temporal frequencies in a three-dimensional surface plot for PD Patient 2 who shows the 'on-off' syndrome. PD Patient 2 is a 46-yr-old man, with an age near that of the mean of the normal observers. Snellen visual acuity was 20/20 and 20/30. A represents the three-dimensional surface measured when this patient was in the 'on' phase and B the surface measured when this patient was in the 'off' phase. Since this patient serves as his own control by providing data in both 'on' and 'off' periods, C shows the 'difference' three-dimensional surface resulting when the 'off' phase responses are subtracted from the 'on' phase responses. The shape of the difference surface suggests that dopamine enhances sensitivity at the peak of the spatiotemporal surface and attenuates sensitivity at the lower spatial frequencies (*see text*).

in the visual system. The data in fig. 5 also include the 'on' vs 'off' sensitivity 'difference'. On the 'difference' surface, notice that (1) there is a valley rather than a peak and (2) the edges dip slightly *below* the surface. An almost identical surface was obtained in 4 out of the 7 eyes. This 'difference' surface leads us to suggest that the effect of dopamine at low spatial and temporal frequencies is to decrease contrast sensitivity, and that the effect of dopamine at the peak of the S-T surface (and beyond) is to enhance contrast sensitivity. Thus these data suggest that dopamine is involved in low frequency attenuation and medium and high frequency amplification (i.e., tuning) of human S-T contrast vision.

### DISCUSSION

Over the last several years, CS testing has proved to be a useful diagnostic tool of visual disorders (for review, *see* Bodis-Wollner and Camisa, 1980). However, similar CS alterations may occur with different pathologies. The present data suggest that in patients with PD who are receiving dopamine precursor therapy on a regular schedule, combining spatial CS testing with flicker sensitivity testing reveals a characteristic, and perhaps specific, abnormality. In PD, progression occurs as a result of the continued loss of dopaminergic neurons. Apparently, in addition to motor impairment, vision is also affected. Visual dysfunction in PD cannot be characterized simply by a sensitivity loss; rather, the shape of the function is abnormal. In PD, when a low temporal frequency of modulation is employed, there is only a modest sensitivity increase with increasing spatial frequency of the pattern (i.e., a lack of tuning). Conversely, there is a lack of sensitivity enhancement of low spatial frequencies with increasing rates of temporal modulation. It is possible to argue that these results—attenuation of peak sensitivity and an apparent lack of low spatial frequency attenuation—represent a down and leftward shift of the complete CS function, similar to what could occur with eccentric viewing and/or reduced mean luminance. There was no evidence of eccentric viewing in the patients that we studied. There was no evidence of miotic pupils to account for decreased mean luminance. It is conceivable, however, that a lack of dopamine may lead to a loss of light sensitivity which could, in turn, result in a CS function that is characteristic of reduced mean luminance. This hypothesis could be supported by recent data in invertebrates, but as we shall point out, other invertebrate data support the notion that dopamine is involved in receptive field tuning. At this point, therefore, it is impossible to decide which is the more physiologically meaningful characterization of the S-T loss in patients with PD. Importantly, in patients with the 'on-off' syndrome, the characteristic abnormality is prominent during the 'off' phase, while sensitivity measured during the 'on' phase falls closer to the normal limits of responses. These results suggest that the change in S-T CS represents changes in spatiotemporal tuning which are linked to a deficiency of dopamine (DA) in the CNS.

The 'parkinsonian' type of CS distortion has not been shown in other disorders.

Most forms of macular pathology predominantly lower the CS curve and attenuate high frequency responses without affecting the shape of the function (Wolkstein *et al.*, 1980). In primary open angle glaucoma, predominant low spatial frequency impairment occurs, while peak and high spatial frequency sensitivity is less affected (Atkin *et al.*, 1979). In patients with space-occupying or vascular cerebral lesions, sensitivity to low frequency patterns is rarely, if ever, affected more than sensitivity to the high spatial frequencies (Bodis-Wollner and Diamond, 1976). In patients with multiple sclerosis (MS) and demyelinating optic neuropathy, selective impairment of contrast sensitivity to any part of the spatial frequency curve may occur (Regan *et al.*, 1977; Bodis-Wollner *et al.*, 1978). When S-T CS is measured in optic neuropathy, some patients show a selective spatial frequency loss which occurs irrespective of temporal modulation (Hess and Plant, 1983), while other optic neuritis patients exhibit spatiotemporal abnormalities despite normal responses to stationary gratings (Marx *et al.*, 1984; Medjbeur and Tulunay-Keesey, 1985). Medjbeur and Tulunay-Keesey (1985) have shown that with higher rates of temporal modulation CS losses may become worse in some patients with MS, may show no change in other patients with MS, or become apparent only with temporal modulation in still other patients with MS; moreover, none of the patients in this study showed a preferential temporal frequency-dependent loss at low spatial frequencies. Nissen *et al.* (1985) reported low spatial frequency losses in one out of 14 patients suffering from Alzheimer's disease. No data are available concerning the effect of temporal modulation in the CS loss in this patient. Finally, Domenici *et al.* (1985a) reported the effect of dopaminergic therapy on spatial CS in normal volunteers. Their data concerning the effect of DA on human vision are in broad agreement with our results in PD and DA deficiency. Domenici *et al.* (1985b) have also published data concerning CS changes in 6 patients severely affected by PD. All the patients showed a lack of peak sensitivity to medium spatial frequency patterns and some general depression, as our results also reveal. Very recently, Regan and Maxner (1987) reported pronounced spatial CS losses in patients with PD when a 2 cpd pattern was presented between 4 and 8 Hz. These data also revealed orientation-selective losses which we did not explore. However, the two sets of data are in broad agreement concerning S-T dependent CS loss in patients with PD.

We have shown that specific CS changes occur in many patients with PD. Overall, the data obtained in more than half of the eyes of these patients with stable signs of PD show changes which are essentially similar to those seen in the 'off' stage of the patients with the 'on-off' syndrome (i.e., those patients with PD who serve as their own controls). In patients with the 'on-off' syndrome, we have observed that the specific CS deficit improves along with an improvement in motor symptoms. This result suggests that the CS improvement is due to restored DA efficiency, a result similar to that reported by Domenici *et al.* (1985b). Hence the results obtained in the bulk of these patients with PD, which are comparable to those observed in the 'off' stage of the 'on-off' patients, suggest that the CS deficit is caused by DA

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frequencies. Furthermore, there is impaired temporal frequency tuning in PD. We propose that PD not only affects the visual system but, specifically, that it affects receptive field organization in the human visual pathway.

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## OMNIPAUSE NEURONS IN TWO CASES OF OPSOCLONUS ASSOCIATED WITH OAT CELL CARCINOMA OF THE LUNG

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### SUMMARY

Opsoclonus is an involuntary eye movement disorder in which there are chaotic, usually conjugate, multidimensional saccadic eye movements. In this paper 2 cases of opsoclonus are reported, as a paraneoplastic phenomenon in association with oat cell carcinoma of the lung. It has previously been hypothesized that opsoclonus results from dysfunction of a group of premotor neurons in the brainstem called omnipause neurons. We describe the location of these cells in man by homology with animal studies, and describe the light microscopic appearance of these neurons in the 2 cases of opsoclonus. Although these neurons appeared normal it is still possible that their function was disturbed as a result of metabolic or neurotransmitter abnormalities.

### INTRODUCTION

Opsoclonus is an eye movement disorder characterized by involuntary chaotic multidirectional saccades without an intersaccadic interval, that are usually conjugate (Vignaendra and Lim, 1977). It may occur either alone or in association with myoclonus and ataxia (the opsoclonus syndrome). The aetiology is very varied but the disorder is most commonly seen in the setting of either a nonspecific viral (Cogan, 1968), postviral (Baringer *et al.*, 1968) or bacterial illness, or as a paraneoplastic syndrome in children with neuroblastoma (Solomon *et al.*, 1968) or in adults with carcinoma (Sheinman and Gawler, 1982).

Considerable interest in recent years has been focused on the premotor neural network concerned with the generation of saccades which lies predominantly in the paramedian pontine reticular formation (PPRF). Two cell types found in this region are the burst neurons and the pause neurons. The burst neurons are active before saccades and carry information specifying the parameters of the subsequent eye saccades. Pause neurons are cells whose on-going activity is interrupted before saccades. They pause either before eye movements in a specific direction (directional

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pause neurons) or before eye movements in all directions (omnipause neurons). The omnipause neurons have a high on-going firing rate and exert a tonic inhibition on some of the burst neurons, so releasing this inhibition and allowing these bursters to activate the eye muscle motor neurons appropriately for a saccade. Thus the omnipause neurons act as a gate, or a trigger for saccades (Keller, 1974, 1981; Robinson, 1975; King and Fuchs, 1979; *see Fuchs et al.*, 1985, for review).

In an attempt to model this brainstem neural network, Zee and Robinson (1979) concluded that 'whenever oscillations consist of to-and-fro saccades without an intersaccadic interval they most likely reflect instability of the pulse generator itself and specify a disorder of the mechanisms by which pause cells control burst neurons'. Opsoclonus is such a saccadic oscillation and confirmation of such a hypothesis demands evidence of pause cell dysfunction in this condition. Analysis of the various autopsied cases of opsoclonus (reviewed in Wertenbaker *et al.*, 1981; Kilgo and Schwartz, 1984; Digre, 1986) has shown a considerable variability both in anatomical localization and in the extent of the pathological abnormality. Since the publication of these reports the anatomical localization of omnipause cells has been identified in the monkey and homologous cell groups found in the human brainstem (Büttner-Ennever and Pause, 1985; Büttner-Ennever *et al.*, 1987) and in this report we describe the pathological findings in 2 cases of opsoclonus secondary to an underlying carcinoma of the lung. Particular attention is given to an examination of the area of the PPRF which is homologous to the omnipause cell area in the monkey.

## CASE REPORTS

### *Case 1*

The patient, a 69-year-old man who had previously been a heavy smoker, presented in June 1983 with a 1 month history of brief episodes of vertigo and diplopia. He was found to be hypertensive and treated with hydralazine, spironolactone, aspirin on alternate days, and dipyridamole. The vertigo worsened and progressive unsteadiness of gait developed. By September 1983 his gait was markedly unsteady, and when standing or attempting to stand, jerky myoclonic movements of the neck, trunk and limbs would build up and he would begin to shake uncontrollably. These involuntary movements would subside on lying down. Speech was not dysarthric, and there was little inco-ordination of the limbs, but horizontal nystagmus was present on lateral gaze to either side with vertical nystagmus on downgaze. All of the tendon jerks were present and the plantar responses were flexor. Chest x-ray, CT head scan and CSF examination were normal.

During the next 2 weeks, the vertigo, truncal ataxia and nystagmus increased, and the patient became restless. Repeat CT head scan carried out under general anaesthesia (nitrous oxide and oxygen) was again normal. The anaesthetic procedure was unremarkable but over the course of the next few days, the patient became so ataxic that even sitting up in bed was impossible, and it was noted that the nystagmus had been replaced by opsoclonus. Ocular flutter was not noted when the nystagmus changed to opsoclonus. The opsoclonic movements consisted of rapid conjugate oscillations of varying amplitude in all directions. These movements were present at rest and in all directions of gaze, with a rotatory component on upgaze. They were present almost continuously and interrupted smooth pursuit and refixation saccadic eye movements. The globes continued to oscillate when the eyes were closed. The pupils were normal.

Repeat CSF examination revealed 18 leucocytes/ml, mainly lymphocytes with some macrophages but not malignant cells. The protein content was 0.85 g/l. CSF sugar and microbiological studies, including virological culture and viral antibody screen, were normal, but Link's IgG index was elevated at 0.78 (normal upper limit 0.58) and oligoclonal IgG bands were present. Blood examination was normal apart from a slight increase in the gamma region on protein electrophoresis, but quantitative immunoglobulin assay and serum complement levels were normal. A serum auto-antibody screen, which did not include nervous system tissue, was also normal. An EEG revealed a mild diffuse cerebral disturbance but no specific features, nor any change in cerebral activity during the myoclonic limb movements.

Clonazepam and sodium valproate failed to control the myoclonus, but corticosteroids were not given, and over the next few weeks the myoclonus improved, although the opsoclonus and ataxia persisted, as did intractable vertigo. The neurological picture remained unchanged over the ensuing months with gross truncal ataxia, opsoclonus and occasional myoclonic leg jerks until fatal bronchopneumonia supervened in March 1984, 10 months after the patient first presented, and 7 months after the onset of opsoclonus. At no time throughout the illness was palatal myoclonus observed.

### *Case 2*

The patient, a 56-year-old man, who was a heavy smoker, presented in November 1984 with blurring of vision followed 3 days later by unsteadiness, vomiting and some confusion. He was admitted to hospital after 4 days when he had become more ataxic. In addition it was noticed that his eyes were making random conjugate jerky movements and that he was dysarthric. When seen 2 weeks later he had opsoclonus, spontaneous irregular myoclonic jerks affecting all four limbs and was markedly ataxic. The opsoclonus was present when his eyes were fixating an object, at the termination of a refixation saccade, and interrupted smooth pursuit eye movements. A CSF examination revealed 25 leucocytes/ml mainly lymphocytes, and a protein content of 0.7 g/l.

His condition deteriorated with continuing vomiting and gross myoclonus and he was transferred to the London Hospital 3 days later. On examination he was semicomatose, and dyspnoeic at rest with poor chest expansion. He moved his limbs equally to peripheral painful stimulation; the tendon reflexes were normal and the plantar responses flexor. There was continuous opsoclonus with limb myoclonus, the two being temporally independent. Because of his poor respiratory effort he was transferred to the Intensive Care Unit where he was ventilated. A repeat CSF examination showed no change, and in addition CSF sugar, microbiological studies, including virological culture, and viral antibody screen, were normal, but Link's IgG index was elevated at 1.03 and oligoclonal IgG bands were present. Blood examination confirmed the clinical impression that he was dehydrated and his peripheral leucocyte count was raised 14.5 cells/ml which persisted throughout his illness. An EEG showed a diffuse bilateral cerebral disturbance and there was no clear response to auditory, tactile or painful stimuli. An enhanced CT scan did not show any abnormality.

Ventilation was required for 4 weeks and his opsoclonus and myoclonus were treated with corticosteroids, thiamine, sodium valproate and a course of plasma exchange without benefit. Large doses of benzodiazepines, clonazepam or diazepam did reduce the myoclonus, but only in a dose which resulted in marked sedation. Although the chest x-ray showed a slightly widened mediastinum, bronchoscopy on two occasions was normal. Eventually a scalene lymph node biopsy was taken which revealed infiltration by small cell (oat cell) carcinoma. His condition gradually deteriorated and he died 3 months after the onset of the disorder.

## AUTOPSY FINDINGS

*Case 1*

Routine autopsy identified a pea-sized lesion in the left lower bronchus, and enlargement of the left hilar lymph nodes which were replaced by tumour. Tumour was not found outside the thorax. Microscopically the lesion in the left lower bronchus and the hilar tumour proved to be an oat-cell carcinoma.

The brain weighed 1460 g and appeared normal, both on external examination and on slicing. No microscopic abnormality was observed in the cerebral hemispheres. Serial sections of the midbrain,



FIG. 1. Photomicrograph of inferior olivary nucleus (*Case 1*) showing a complete loss of neurons. Luxol fast blue,  $\times 25$ .

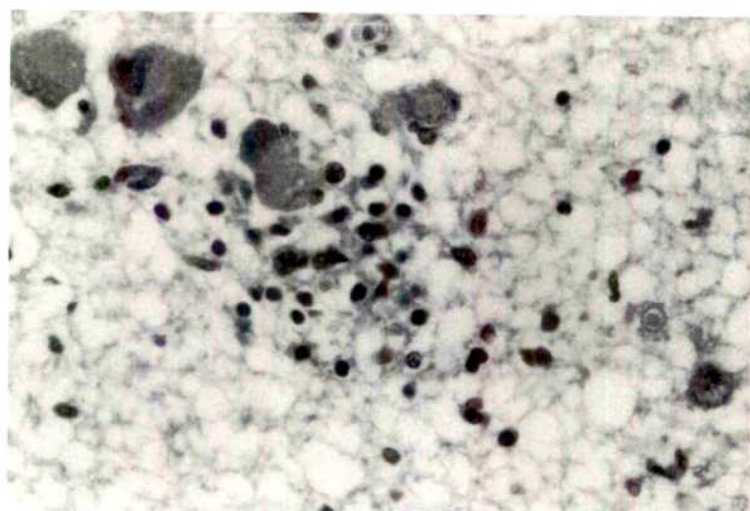


FIG. 2. Photomicrograph of neurons in periaqueductal grey matter (*Case 1*) showing collections of lymphocytes. Haematoxylin and eosin,  $\times 300$ .



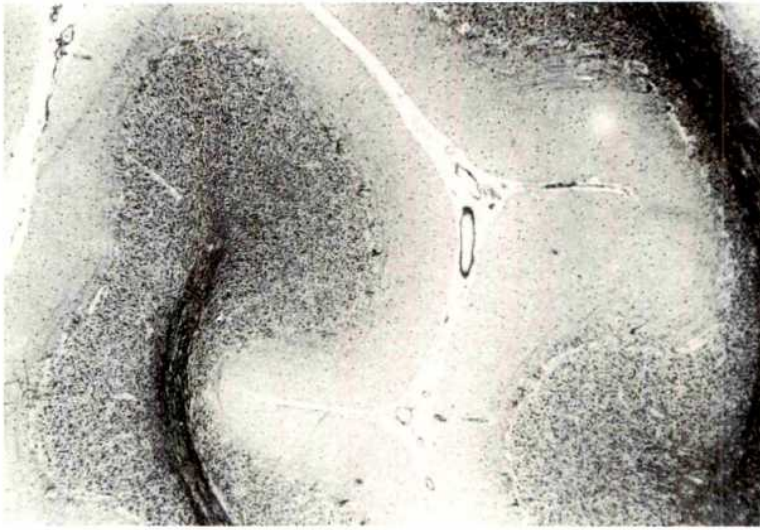


FIG. 3. Photomicrograph of cerebellum (*Case 1*) showing a marked reduction in the number of Purkinje neurons. Luxol fast blue,  $\times 50$ .

pons and medulla, however, showed complete loss of neurons from the inferior olivary nuclei, which were gliotic (fig. 1). Scattered lymphocytic perivascular cuffing was present in the midbrain and pons and small collections of lymphocytes unrelated to blood vessels were noted in the periaqueductal grey matter (fig. 2). The left vestibular nucleus contained a small haemorrhage. The medial longitudinal fasciculus, central tegmental tract and the third, fourth and sixth cranial nerve nuclei were normal. Examination of the cerebellum revealed loss of more than half of the Purkinje neurons (fig. 3), but no changes were observed in the other cortical layers, nor in the cerebellar nuclei or white matter.

Examination of the nucleus raphe interpositus revealed a full complement of omnipause cells of normal appearance (fig. 4).

#### *Case 2*

Routine autopsy revealed multiple enlarged mediastinal nodes and multiple deposits of firm white tumour in the liver, which microscopically proved to be oat-cell carcinoma. No primary tumour site was found in the lung.

The brain weighed 1374 g and appeared normal both on external examination and on slicing. No microscopic abnormality was observed in the cerebral hemispheres or cerebellum, or on examination of the serial sections of the midbrain, pons and medulla. A complete examination of the nucleus raphe interpositus was not possible, but a full complement of omnipause cells of normal appearance was seen in two sections.

### DISCUSSION

Pathological studies have shed little light on the cause of the opsoclonus syndrome. The rare fatal encephalitic cases have usually shown only mild lymphocytic cuffing in the brainstem, cerebellum, diencephalon or basal ganglia (Cogan, 1954; Wertenbaker *et al.*, 1981). Childhood neuroblastoma cases have also yielded little morphological information except for possible loss of Purkinje cells (Henson and Ulrich, 1982). Four cases of adult paraneoplastic opsoclonus have





FIG. 4. A, transverse section from the brainstem of Case 1 at the level of the abducens nucleus (nVI). The abducens rootlets (NVI) lie lateral to the omnipause region which is marked by an arrow; the cell group is termed nucleus raphe interpositus (rip). Facial nucleus (NVII), medial longitudinal fasciculus (MLF), pontine nuclei (pn), pyramidal tract (PT), nucleus reticularis gigantocellularis (gc). Luxol fast blue and cresyl violet; bar = 2 mm. B, section through rip to show typical cells with long horizontal dendrites (arrows). Dotted line marks midline. Haematoxylin and eosin; bar = 500  $\mu$ m. C, Palmgren stained section of rip (arrow as in B).

been examined at postmortem. The tumours were a uterine carcinoma (Alessi, 1940), an undifferentiated adenocarcinoma of lung (Ross and Zeman, 1967), a breast adenocarcinoma (Ellenberger *et al.*, 1968), and an oatcell carcinoma of lung (Graus *et al.*, 1984). A further case, with a history of uterine cancer but no clinical evidence of recurrence and in which postmortem examination was limited to the cranial contents, was reported by Kilgo and Schwartz (1984). Histological changes in these cases consisted of slight perivascular round cell infiltrates of the brainstem or meninges overlying the cerebellum associated, in three instances, with mild to severe loss of Purkinje cells and changes in the dentate nucleus or peridentatal demyelination. Cerebellar pathology, however, has not been a consistent feature either of the paraneoplastic or encephalitic groups, neither of which has shown any definite pattern of microscopic involvement to account for the clinical features.

The present cases, like those already reported, failed to identify the anatomical basis of the opsoclonus and myoclonus. In the pathological examination of our 2 cases, particular attention was given to the nucleus raphe interpositus in the pons, the area considered to contain omnipause neurons which according to Zee and Robinson (1979) may be involved in the generation of opsoclonus.

In the monkey, omnipause neurons are found clustered around the midline of the paramedian pontine reticular formation (PPRF) (Keller, 1974, 1981; Raybourn and Keller, 1977; Evinger *et al.*, 1980; Nakao *et al.*, 1980), in a circumscribed area at the pontomedullary border, often called the 'omnipause region'. The connections to and from the omnipause region have been extensively studied (Raybourn and Keller, 1977; Evinger *et al.*, 1980; King *et al.*, 1980; Nakao *et al.*, 1980; Kaneko and Fuchs, 1982; Langer and Kaneko, 1983, 1984). Despite these reports, which describe omnipause neurons as a compact cell group and, functionally, highly differentiated, it has only recently proved possible to identify the omnipause neurons in standard cresyl violet-stained material as a clear cytoarchitectural entity, and then only in monkey and man (Büttner-Ennever *et al.*, 1987). In the latter study, omnipause neurons were located in the awake monkey with a recording electrode and marking lesions were made at the recording sites. In addition, injections of anterograde tracer substances were placed in the superior colliculus, a structure known to make monosynaptic contacts with omnipause neurons (Harting, 1977; Raybourn and Keller, 1977). The location of the marking lesions, and the labelled terminals of superior colliculus efferents in the caudal pons, were compared with the detailed cytoarchitecture of the omnipause region. The results showed that the omnipause neurons in the monkey lie in a morphologically and functionally distinct division of the raphe cell column in the caudal pons just caudal to the nucleus raphe pontis. The name given to this cell group is nucleus raphe interpositus. The main features of nucleus raphe interpositus cells, which distinguish them from the nuclei raphe pontis and magnus, are their orderly arrangement around the midline, their highly developed horizontal dendrites which often spread over the midline, and their high content of cytochrome oxidase compared with the surrounding neuropil.

Using these criteria it is possible to identify a homologous cell group in the human brainstem. In fact this cell group, which lies in the nucleus pontis centralis caudalis, close to the midline between the rootlets of the abducens nerve, was already described by Olszewski and Baxter in 1954 in their painstaking analysis of the reticular formation (*see* Plate XXIII and p. 168 of Olszewski and Baxter, 1954).

In both of the present cases, the cells in the nucleus raphe interpositus were of normal size and number. This lack of microscopic evidence of abnormality in the omnipause cells does not, of course, prove that they were functioning normally. It is well recognized that neuronal dysfunction due to an abnormality of the afferent inputs, metabolic or neurotransmitter disturbances may be present in areas of the brain without the presence of microscopic neuronal abnormalities.

Turning now to the possible relevance of the remaining autopsy findings, the sparsity and diversity of the lesions observed in Case I precludes clinicopathological correlation. The significance of the striking involvement of the inferior olivary nuclei is uncertain. Lymphocytic cuffing and neuronal loss in the inferior olives is a frequent finding in brainstem carcinomatous encephalomyelitis according to Henson and Urich (1982), who also mention opsoclonus and myoclonus, but do not discuss clinicopathological correlation. Olivary involvement, however, is unlikely to be important in causing the opsoclonus syndrome since it has not been a notable feature of previous cases that have specifically reported opsoclonus. Moreover, the type of involuntary movement normally associated with inferior olivary nuclear damage, namely palatal myoclonus (Gautier and Blackwood, 1961), was absent.

Nevertheless, the possible relevance of the olivocerebellar pathway and the loss of Purkinje cells observed in several cases should not be completely dismissed. Indeed some reports have incriminated the cerebellum as the cause of opsoclonus (Ellenberger *et al.*, 1968; Ziter *et al.*, 1979). Hepp *et al.* (1982) considered that the cerebellar nuclei exerted an important influence on the execution of saccadic eye movement. This is conjectural, but the association of cerebellar degeneration and myoclonus in disorders such as the Ramsay Hunt syndrome provides grounds for considering that the cerebellum may play a part in producing the myoclonus of the opsoclonus syndrome. One possible mechanism would be loss of cerebellar inhibition to the brainstem reticular formation, as in posthypoxic action myoclonus (Halliday, 1967; Marsden *et al.*, 1982). The absence of EEG changes during the myoclonic jerks in the infants reported by Kinsbourne (1962) and the present cases, suggests that the myoclonus associated with opsoclonus may also be reticular, but further electrophysiological studies would be needed to show this. Brainstem reticular involvement might also explain the unusual shivering or shuddering body tremors of some cases (Brumlik and Means, 1969).

The cause of the pathological damage in the opsoclonus syndrome is also uncertain. Encephalitic cases usually occur in relation to an upper respiratory or gastrointestinal infection, but no specific virus has been identified (Kilgo and Schwartze, 1984). An immunological disorder (Wertenbaker *et al.*, 1981) has been

proposed on the basis of indirect evidence such as CSF plasmacytosis with elevated gamma globulin levels (Dyken and Kolář, 1968), and the apparently favourable response of some cases to ACTH or corticosteroids (Kinsbourne, 1962). Immunofluorescent antibodies to guinea pig Purkinje and rat peripheral nerve axons have been reported in a 10-month-old boy with parainfectious opsoclonus (Cawley *et al.*, 1984), but no such antibodies were detected in a patient with oatcell carcinoma of lung reported by Graus *et al.* (1984). Antibodies against nervous system were not sought in the present cases, but oligoclonal bands were present in the CSF, suggesting local IgG synthesis. Whether the reported immunological changes are specific and directed against a virus or against tumour-cell antigens that are shared by nerve cells, or whether the findings are a nonspecific response to tissue damage produced in some other way is not known. A disturbance of thiamine metabolism was proposed by Nausieda *et al.* (1981) who noted improvement of opsoclonus in a patient with an anaplastic bronchogenic carcinoma given thiamine, but thiamine did not help the patient reported by Kilgo and Schwartz (1984) or our Case 2. A variety of toxins and drugs such as lithium, haloperidol, thallium and amitriptyline have been reported to cause opsoclonus (Kilgo and Schwartz, 1984). So far as we are aware, it has not been reported with hydralazine, spironolactone or the anaesthetic agent which our Case 1 received.

Seventy years after Orzechowski and Walichiewicz (1913) originally described the opsoclonus syndrome, its pathophysiology remains an intriguing enigma. Autopsy studies have so far contributed little, suggesting that traditional neuropathological methods of examination may be inadequate for the task. To proceed further, newer techniques, electrophysiological as well as pathological, are likely to prove necessary.

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## BOOK REVIEWS

**Philosophy and the Brain.** By J. Z. Young. 1987. Pp. 233. Oxford: Oxford University Press. Price £12.95.

*Philosophy and the Brain* had its origins in a series of lectures given in 1982 in the Departments of Philosophy and the History and Philosophy of Science at University College London. These were entitled 'Philosophers use your Brains'. Professor Young decided that this title was too abrasive for the resultant book, but the message remains. Philosophers tend to consider the phenomena of mind in isolation from brain. As J. Z. Young points out, the word 'brain' does not appear in the index of Gilbert Ryle's *The Concept of Mind*. A major component of *Philosophy and the Brain* is therefore an exposition of current views on the organization of the nervous system, particularly as this relates to cognitive function. 'What's in a brain?' he asks. In answering this, Professor Young explores similar territory to that covered by J.-P. Changeux in *Neuronal Man: the Biology of Mind*, a book that deserved more attention than it received.

*Philosophy and the Brain* is included in the series of OPUS books which are directed towards the general reader and students. A degree of simplification is thus inevitable, but neurologists may squirm slightly at statements that patients with unilateral lesions of the visual cortex are blind 'in the opposite eye'; that a patient with a right parietal lesion developed right-sided hemi-inattention; or that the striatum is 'relatively small'.

The major thesis expounded, namely that mental activity is inseparable from the brain, would be contradicted by few neurologists. Attempts to explain 'brain-mind' relationships in terms of the three worlds of Popper and Eccles would evoke little sympathy. Nor do they in Professor Young. Throughout the book, he firmly bases his approach on a biological viewpoint, that organisms are active self-maintaining systems. 'They are systems with strange properties of acting purposefully, their purpose being to remain organized'. To achieve this end, their brains contain programs that direct such activity, seeking, selecting and extracting information from their environments. For the neuroscientist the problem, as applied to man, is to discover how the brain contains 'representations of all possible states of affairs, including future states, correlated with conscious purposes'. In these terms, J. Z. Young therefore seeks to analyse current knowledge as to cerebral function and the way in which this might provide the basis for cognitive activity. This is written in his characteristic easy and engaging style. He is able to assemble, and present without effort, information from a wide variety of disciplines. Throughout, he relates this to concepts such as Intentionality and valuing that philosophers have raised in their attempts to analyse mind.

Professor Young clearly has a great deal of sympathy with the approach adopted by philosophers and acknowledges that he has always had an interest in philosophy. The concepts are admittedly some of the most difficult with which humanity has wrestled since it began to contemplate its own nature. But has Professor Young perhaps been a little too lenient with the philosophers? For a neurologist, their main fault would seem to lie in their attempts to solve the problems of mental activity by introspection and the analysis of the words that we use to describe the conclusions derived from such forays into our inner mental life. Yet it is becoming increasingly clear that significant aspects of cognitive processing are 'unconscious' and inaccessible to introspection. What is necessary is the detailed study of the location, timing and sequencing of the cerebral events that underlie



cognition. These are now beginning to become amenable to experimental analysis, for example by dynamic in vitro imaging techniques and the recording of event-related cerebral potentials.

When this is done, surprising results that could not be predicted by introspection may emerge. Thus Libet and others, in a study on the timing of conscious intention to act (*Brain*, 106, 623) to which Professor Young made appropriate reference, found that the 'readiness potential' (Bereitsschaftspotential) regularly *precedes* the feeling that an individual experiences when he decides to perform a voluntary movement. This startling result suggests that the brain has already initiated the movement when the subject decides that he will undertake it. Consciousness, in this situation, is perhaps acting as a monitor, giving an illusory sensation of volition. How central, then, is consciousness in the organization of volitional behaviour?

J. Z. Young substitutes 'Cogito ergo sum'—'I think, therefore I am'—with the more biological proposition 'I am certain that I am alive'. This is the central fact of human experience. In the ultimate analysis, organisms are containers for DNA and brains are control mechanisms for some of these containers. 'DNA est, ergo sum' might be more appropriate. How the evolution of consciousness assists the brain in contributing to the survival of organisms is an unsolved mystery. But Professor Young is fully justified for calling the philosophers to task for ignoring the brain in their efforts to solve the problem of Mind.



P. K. THOMAS

**Parkinson's Disease.** *Advances in Neurology*, Volume 45. Edited by Melvin D. Yahr and Kenneth J. Bergmann. 1986. Pp. 680. New York: Raven Press. Price \$113.50.

Since 1982 seven of the eleven volumes of *Advances in Neurology* have related to movement disorders which reflect the considerable recent interest in these areas. This latest volume represents the Proceedings of the 8th International Symposium on Parkinson's Disease held in New York in June 1985, which was organized by the Research Committee on Extrapyrarnidal Disease of the World Federation of Neurology. The book follows the organization of the Conference programme which covered four major themes: epidemiological and aetiological factors; biochemical and ultrastructural pathology; motor and nonmotor aspects of Parkinson's disease; and current and future approaches to therapy. A wide spectrum of subjects is discussed with some 110 presentations, although the substantial sections on the neurotoxin MTPT and on cognitive abnormalities in Parkinson's disease reflect areas of particular advance in the last three to four years. However, perhaps inevitably with Conference proceedings, there is considerable variability in style and content of the individual chapters. In the preface the editors state that participants were invited to present an overall review of current developments as well as the directions and results of their own studies. This has been interpreted variously with some chapters that are predominantly review articles and some that are little more than brief research communications. In general it has been the review chapters that have proved the most interesting on reading this book. Of particular note are those on biochemical pathophysiology by Hornykiewicz, MPTP by Kopin, progressive supranuclear palsy by Agid and the discussion of cognitive impairment by Growden and Corkin. Other valuable chapters are those which bring together disparate observations in the literature in order to discuss abnormalities in the respiratory and visual systems and papers dealing with specific clinical aspects such as foot dystonia, pain and depression in Parkinson's disease. The other common problems facing clinicians managing Parkinson's disease such as bladder disturbance and hallucinosis, both deserve greater coverage.

This volume carries the mark of conference proceedings with some duplication, variability and lack of coherence between the different chapters. At times the variability and apparent lack of editorial scrutiny can be irritating. For example, in the first chapter the abbreviation SP is used both for the senile plaque and substance P and a general inconsistency of abbreviations is found throughout.



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technique and CT protocols, which include use of the dynamic mode and reasons for superiority of coronal sectioning in most cases of microadenoma.

In the rest of the text, the various disease processes are considered on a regional basis. There are chapters on the effects of pregnancy, dopamine antagonists and surgery. It is, perhaps, unfortunate that the authors do not formally address the doubts expressed in the recent literature regarding the accuracy of computed tomography relative to surgical localization of small microadenomas: doubtless in most instances the quality of the radiology on which such assessments have been based does not approach the rigorous standards set by the authors.

The book is profusely illustrated, with well annotated images of excellent quality. The figures for each chapter are gathered together and in all instances proof is offered for the accuracy of the authors' deductions, so that the work can be used as an atlas without reference to the text.

References to the literature are up to date and comprehensive and the index is good. The book is strongly recommended both for reference and basic instruction to all undertaking and interpreting computed tomograms of the pituitary region.

BRIAN KENDALL

**Visual Neuroscience.** Edited by J.D. Pettigrew, K.J. Sanderson and W.R. Levick. Cambridge University Press. 1986. Pp. 448. Price £75.00.

*Visual Neuroscience* attempts two things, to celebrate P.O. Bishop's contribution to the study of vision and to provide an integrated account of what is now called visual neuroscience. In attempting to kill two birds with one stone it scores one direct hit and a glancing blow, which is above average marksmanship. The bull's eye was the celebration. P.O. Bishop has had and is continuing a long and distinguished career in visual neurophysiology. He is noted for his quantitative methods, relentless insistence on precisely defining commonly used terms like disparity and receptive field, for his ability to stick with a problem for many years, and of course for his many discoveries in the field of binocular vision. Additionally there is his influence on a large group of visual scientists, many of whom worked in his laboratory and now direct laboratories of their own in many countries. His influence has been extensive. Quite rightly the group of scientists who met on Lord Howe Island in 1982, in what the preface describes as a 'family style celebration', knew him well or had been influenced by him, or both. Not surprisingly their chapters highlight Bishop's own wide-ranging interests, and their autobiographical sketches at the end of the book are of real historical interest for the light they throw on Bishop's personality and the way in which he inspired and nurtured so many young colleagues. Episodic memory is so vivid that we easily forget that it is private and dies with us, unless recorded. This book attractively and importantly records Bishop's direct and indirect influence on major topics such as, to name only a few, the schematic eye, receptive field disparity, intrageniculate inhibition, and end-stopping in the receptive fields of cortical cells. Three cheers for all this.

Not so many cheers for the book as an account, at any level, of what its title boldly implies. There are 27 chapters, grouped under The Retina; Retino-geniculate Connections; Visual Development; Comparative Visual Physiology; Visual Cortex; Integrative Aspects. Within these groups the emphasis is on matters close to Bishop's own interests, e.g., optics, structure/function relationships, the primary visual pathway to the lateral geniculate nucleus and thence to visual cortex, how a cell obtains its receptive field properties, binocular vision, parallel and serial processing. Furthermore, these topics are approached chiefly by electrophysiological and neuroanatomical methods. The book scarcely mentions topics such as colour vision, interhemispheric integration, selective visual attention, any kind of visual behaviour other than that studied by rigorous psychophysics, any of the many other pathways from the retina into the brain, how we see when the eyes or body move, neuropsychological studies of vision, computational approaches. Also absent are accounts of the use of modern techniques such as immunocytochemistry, brain imaging, selective application and uptake of putative neurotransmitters, molecular methods. None of these omissions is important if the book is seen primarily as a Festschrift. But they are regrettable if the editors intended to cover the field implied by the title.

How good a book is it if one forgets its social purpose in commemorating Bishop and recognizes that the title is misleading? The answer is that it is a mixed bag. There are only 3 chapters on visual development and each is specialized. As a result, this popular and productive area of research is misrepresented by omission. There are 5 chapters on visual cortex, of which those by Henry (on streaming) by Kaas (on structural basis for information processing) and by Dreher (thalamocortical and corticocortical interconnections) are broad ranging and useful reviews. Okawa, Kato and Ito are more specialized in reviewing evidence for GABAergic intracortical inhibition, and even narrower in evaluating only electrophysiological evidence. Bullier's lengthy chapter on bifurcating axons is attractively written, but the inclusion of such an esoteric topic to the exclusion of say, colour, highlights the idiosyncrasy of much of the book. Nevertheless, the group of chapters on visual cortex does cohere. There are 6 chapters on the retina, although the last, on controlling intensity in a stimulator, is a brief technical note whose presence is mystifying until one remembers the first purpose of this book. This group contains three of the most outstanding contributions. Barlow takes us back to basics and asks why the eye can't see better, Wässle succinctly summarizes distinguished work on types of ganglion cells and the concept of coverage, and Hughes manages to explain the incomprehensible in describing the schematic eye and showing why it is so useful. Retinogeniculate connections are described in 3 chapters, but why oh why are they exclusively devoted to the cat when so much is now known about the monkey? Comparative visual physiology attracts 4 chapters but only 1 compares vision with any other sense, and another is confined to the lateral geniculate nucleus. The chapter on mammalian evolution is anatomical not physiological. Pettigrew's chapter on the evolution of binocular vision is arguably the most successful of the group. It asks basic questions, such as why it is advantageous to have overlapping visual fields, and answers them with evidence from widely separated species and techniques. The final group of chapters, on Integrative Aspects, is not an unqualified success, despite containing 2 gems. Illusory contours are intriguing and may yet prove to be important, but so far they are not sufficiently central to considerations of integration to justify two chapters. Nor are hallucinations. Feature vs Fourier analysis may not be the sharp dichotomy that Kulikowski and Kranda present (as MacKay points out elsewhere in the book), but it is widely seen as such and this tightly written chapter repays the effort required to master it. But the prizes here go to Nelson for his entertaining account of unsolved problems of stereopsis, and to the late Donald MacKay for what must be one of his last provocative articles. Like Barlow, MacKay asks what it is that the machinery he is studying is designed to do. For MacKay it is not to generate an explicit internal neuronal representation of the world. Rather, it is to capture optical covariation including the covariation that occurs as a result of eye and body movements. Multiple cortical maps represent an early stage in accomplishing this but do not themselves explain it or even reveal much else that occurs subsequently in nontopographic representations of visual space. Alas, the latter are not discussed in the book.

*Visual Neuroscience* pays proper tribute to P. O. Bishop. With few exceptions it is really a collection of narrow essays on subjects that he or his students and colleagues have worked on during the past thirty years. Some of them are of central importance to visual neuroscience, but many are brief reviews of a fairly narrow area. Furthermore, some closely resemble reviews already published by the same authors. This makes the price of £75 unacceptably steep, even to celebrate such a first rate investigator as Bishop.

ALAN COWEY

**The Physiology and Pathophysiology of the Cerebrospinal Fluid.** By H. Davson, K. Welch and M. B. Segal. 1987. Pp. 1013. Edinburgh: Churchill Livingstone. Price £120.00.

A celebrated emeritus professor of physiology plus one of his former students and an eminent neurosurgeon have joined together to give us a substantial new tome on the physiology and pathophysiology of cerebrospinal fluid.

Over the past twenty years since the book was last revised there has been a vast increase in research activity in the field of the clinical pathology of CSF. I am bound to use the example of the CSF proteins in which no less than three books have appeared in recent years and Davson's text offers 4% of his total pagination to this one topic. This merely illustrates the breadth of the book. Some of the other major topics include: barriers between CSF and blood, acid-base balance, return of CSF to the blood, ontogeny and comparative physiology. On the pathological side there are chapters on: cerebral oedema, barrier destruction and hydrocephalus (both prenatal and acquired). The text is copiously illustrated with helpful diagrams as well as electron micrographs. The work of relevant investigators is briefly summarized and conclusions are offered at the end of appropriate sections. There are over 4,000 references in alphabetical order plus a 15 page index for the 1,000 pages total. Although some might quibble with the price (£120), I cannot imagine anyone who is seriously interested in spinal fluid being without a copy of this now classic opus.

E. J. THOMPSON

**Control of Human Voluntary Movement.** By John C. Rothwell. 1987. Pp. 325. Beckenham, Kent: Green Helm. Price £35.00 (hardback), £17.00 (paperback).

This is a concise survey of the physiology and pathophysiology of human movement. Written by a physiologist working in a clinical environment known for sophisticated studies of movement disorders, it is a nice amalgamation of knowledge derived from human studies and of data from animal experiments necessary for the understanding of human motor control. Clinical observations and recordings from patients with movement disorders are reported as far as they seem relevant for the purpose of this book.

The style and organization of the book and the selection of figures make it a neat and clear guide for the reader. It is short and concise enough to serve as a primer for students, neurologists, clinical neurophysiologists, physiotherapists and many others interested in this topic, and yet contains enough information to be of interest to workers in the field of motor control. I think the book will find a wide readership, since it is a useful introduction to an exciting field of research and application.

HANS-JOACHIM FREUND

**Fast and Slow Chemical Signalling in the Nervous System.** Edited by L. L. Iversen and E. Goodman. 1986. Pp 316. Oxford: Oxford Science (OUP). Price £25.00.

Signalling in the nervous system has long been known to have fast components involving, for example, nicotinic receptors at the mammalian neuromuscular junction and slower components mediated by catecholamines. However, over the past few years there have been enormous advances in the understanding of the mechanisms involved in these two forms of synaptic transmission. The major advances have come with recognition of amino acid transmitters as the main candidates mediating fast transmission in the CNS and secondly, the unravelling of the processes involved in the receptor-activated generation of intracellular second messengers, cyclic AMP and the more recently established candidates, inositol trisphosphate (IP3) and diacylglycerol (DAG) which are likely to mediate slow responses. Each system has demonstrated its own fascinating complexity, with the emergence of two well substantiated processes, the ligand-gated channel located in the post-synaptic membrane that binds amino acid transmitters and the multicomponent adenylate cyclase and polyphosphoinositide systems that mediate slower responses. These and related topics are the subject of this book. The editors are Drs Iversen and Goodman and it is to their great credit that they have attracted such a distinguished collection of contributors who have all made considerable advances in the field.

The progress of research into amino acids is introduced by Krnjević from prehistory, that is before

1950 to the present era, and he lucidly sets the scene for the later chapters on fast signalling. The amino acid transmitter systems are dissected in terms of their electrical and pharmacological effects on neuronal activity. The inhibitory amino acid transmitters, GABA and glycine, have a similar effect producing an increase in chloride conductance and this has been explored by studying their action on chloride channels, channel opening times and single channel conductances. The subject develops from the ion channel to recognition sites for transmitters and allosteric regulatory sites. In particular, the chapters by Krosgaard-Larsen *et al.* and Watkins provide useful reference articles on the molecular pharmacology of GABA and glutamate agonists and antagonists and their comparative biological activity. Benzodiazepine and barbiturate binding sites on the GABA receptor complex are undoubtedly of enormous clinical significance and their properties were interestingly reviewed in Snyder's chapter. The next stage in the assembly of a neurotransmitter system is to look at conducted responses from one neuron to another. This is tackled in an informative chapter by Kelly *et al.* using brain slice preparations (e.g., from hippocampus containing an intact excitatory input) and Sillito studying the response properties of visual cortical cells, the involvement of specific amino transmitters being inferred in each case by the use of selective antagonists.

The effects of neuropeptides, catecholamines, 5-hydroxytryptamine and some of the actions of acetyl choline (muscarinic) which take several seconds to occur, unlike the time scale of fast signals which occur in milliseconds, are the subject of the second section. Studies of these transmitters on the electrical properties of neurons are elucidated by Brown who shows how  $K^+$  and  $Ca^{2+}$  currents are modulated by endogenous transmitters and hence by this mechanism may determine the pattern of discharge of neurons.

The initial action of transmitters mediating slow responses has been shown in a large number of cases to be associated with the modulation of second messenger generation (either an increase or decrease) via a regulatory guanine nucleotide-binding protein (G protein). Subsequently, the second messengers cAMP, DAG or  $Ca^{2+}$  mobilized in response to IP<sub>3</sub> regulate other cellular activities, each being able to activate one or more specific protein kinases responsible for phosphorylating individual protein substrates, for example. The exciting challenges are to understand the complexities of the polyphosphoinositide system responsible for generating IP<sub>3</sub> and other inositol phosphates of unknown function and to identify phosphorylated products and their function. These aspects are admirably covered by Irvine and Berridge and by Walaas *et al.*, respectively.

The complexity of the inositolide signalling system is added to by the coexistence of peptides in neurons with other transmitters and these are comprehensively reviewed by Hökfelt *et al.* This aspect is also more fully developed in the final section by Schmitt who puts forward the hypothesis that apart from classical transmitters, a wide range of 'informational substances' may be influential in neuronal communication. These may reach their targets by diffusion rather than through conventional synaptic connections. However, more conventional pathways are discussed in later chapters finishing with a review by Bloom on the elegant work carried out in his laboratory on cortical organization and the functional interactions between noradrenaline and vasoactive intestinal polypeptide.

This book shows how signalling can be viewed in a number of different ways, the ion conductance changes, ligand binding to receptors, drug modulation of responses, neuronal and nonneuronal pathways and finally their relevance to behaviour and clinical treatment. Very few chapters attempted to bridge these viewpoints. Perhaps if the original meeting on which the book was based had been held in 1987 rather than 1985 we would have seen more emphasis on the molecular biology of receptors. Recombinant DNA techniques have allowed the sequences of GABA and glycine receptor subunits to be determined. Great similarities are shown between the sequences of these receptors in line with their similar effects on chloride conductance. However, more remarkably, considerable homology also exists with another ion-gated channel, the nicotinic receptor, each subunit possessing four transmembrane domains and hence the emergence of a 'super' family of ligand-gated receptor proteins. The finest proof of the authenticity of such a protein comes from the combination of these with electrophysiological techniques, whereby messenger RNA for GABA receptor subunits (alpha

and beta) have been injected into *Xenopus* oocytes and their expression as functional receptors in the membrane monitored by conductance changes in response to GABA.

J. DE BELLEROCHE

**Neuroregulation of Autonomic, Endocrine and Immune Systems.** Edited by Robert C. A. Frederickson, Hugh C. Herdrie, Joseph N. Hingtgen and Morris H. Aprison. 1987. Pp. 691. Dordrecht: Martinus Nijhoff. Price Dfl. 270.00.

Over the last ten years there have been dramatic advances in our understanding of the neural control of many diverse areas of mammalian physiology. This volume represents the proceedings of an international symposium of neurologists, immunologists, psychiatrists and related specialists. It successfully brings together basic science and clinical research over the wide area of nervous control of the endocrine, immunological and autonomic systems.

The individual contributors have presented their topics lucidly and taken the reader rapidly from the background of their subject to the most recent advances. One particular aspect I liked was the 'overview' chapter at the beginning of each section and particularly those by Ganong on the neuroendocrine system and Golub on the immune system.

There can be few, if any, specialities for which this book does not hold some interest. Even respirologists will find the section on neurohumoral mechanisms in asthma and the short communication on sleep apnoea syndromes to keep their interest alive! The book can be highly recommended to anyone with an interest in the relationships of the immune system to endocrine nervous system function but will also be of value to anyone who has a fringe interest in neuroscience and the mechanisms controlling mammalian physiology.

The book is technically well produced. The 26 colour photomicrographs beautifully demonstrate the histochemical distribution of various neurotransmitters, but the cost of £71 is rather high for a photo-offset production.

STAFFORD LIGHTMAN

### **Skull Base Study Group**

The IV International Congress of the Skull Base Study Group will be held in Hannover, FRG, on June 3–6, 1988. The topic of the meeting will be the surgery of the sellar region and the paranasal sinuses. Further information may be obtained from Professor M. Samii, Neurosurgical Clinic, Nordstadt Krankenhaus, Haltenhofstrasse 41, D-3000 Hannover, FRG.

### **Second International Conference on Brain and Spinal Cord Slice Preparations**

A conference on Brain and Spinal Cord Slice Preparations will be held June 15–17, 1988 in Louisville, Kentucky USA. The Conference will address the many new developments, methodologies and applications of CNS slice preparations.

For further information, contact Gerald D. Swim, Director for Continuing Medical Education, School of Medicine, University of Louisville, Louisville, Kentucky 40292, USA.

### **European Neurological Society**

The European Neurological Society (ENS) has been founded to foster cooperation between neurologists and those working in related disciplines within Europe. Meetings will be held biennially. The participation of individuals from other areas of the world is welcomed. The biennial meetings will provide instructional courses for neurologists in training, up-date symposia, and sessions for the presentation of original work, either as platform or poster presentations. The first meeting will be held in Nice from June 19–21, 1988, when the teaching programme will include courses on peripheral neuropathy, neuroimaging, ageing and dementia, and neurovirology/neuroimmunology. There will be symposia on physiological and pathological aspects of cerebral blood flow, clinical neuropharmacology and neurogenetics.

Active membership of the ENS will be by election from clinicians and scientists whose chief interest is directed towards practice, teaching or research in neurology and cognate fields. Active membership will become effective only after contribution to a meeting of the ENS. Junior members may be elected from members engaged in postgraduate studies in neurology or related disciplines.

Further information about the ENS, together with registration and abstract forms for the first meeting, may be obtained from the Secretary, Professor G. Said, Service de Neurologie, Hôpital de Bicêtre, 94287 Le Kremlin Bicêtre Cedex, France. Abstract forms must be returned by February 1, 1988.

### **Fyssen Foundation 1988–1989 Fellowships**

The general aim of the Fyssen Foundation is to encourage all forms of Scientific enquiry into cognitive mechanisms, including thought and reasoning, underlying animal and human behaviour, into their biological and cultural bases and into their phylogenetic and ontogenetic development. For this purpose, the Foundation will award a certain number of fellowships for the training and support of research scientists working in disciplines relevant to the aims of the Foundation such as ethology, palaeontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences.

The fellowships will be granted to French scientists wishing to work abroad and to foreign scientists wishing to work in French laboratories. Study grants will normally be given for one year but may be extended up to three years. Applications should be made on a form obtainable from the foundation and should include a curriculum vitae, a list of the applicant's publications, the names of two senior scientists whom the applicant has asked to send testimonials to the Secretariat of the Foundation, and a letter of acceptance from the inviting laboratory.

Completed applications (15 copies) should be sent to the Secretariat of the Foundation, 194 rue de Rivoli, 75001 Paris. Applications must be received by April 1, 1988.



# BRAIN

## A JOURNAL OF NEUROLOGY

# Brain

## A Journal of Neurology

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# BRAIN

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